

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202714Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 202714

SUPPL # N/A

HFD # 161

Trade Name Kyprolis

Generic Name Carfilzomib

Applicant Name Onyx Pharmaceuticals, Inc.

Approval Date, If Known TBD

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐



IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND #	YES <input type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

Investigation #2		!
		!
IND #	YES <input type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1		!
		!
YES <input type="checkbox"/>		! NO <input type="checkbox"/>
Explain:		! Explain:

Investigation #2

!

!

YES ☐

! NO ☐

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐

NO ☐

If yes, explain:

=====

Name of person completing form: Karen Bengtson

Title: Regulatory Project Manager

Date:

Name of Office/Division Director signing form: Ann Farrell

Title: Acting Director, DHP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KAREN E BENGTSON  
07/20/2012

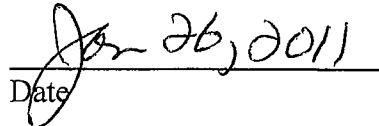
ANN T FARRELL  
07/20/2012

### 1.3.3 Debarment Certification

Onyx Pharmaceuticals, Inc. hereby warrants and represents that it is not debarred under the Federal Food, Drug and Cosmetic Act (FD&C Act) per SEC. 306 [21 USC §335a] and certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



John Bedard  
Vice President, Regulatory Affairs

  
Date

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 202714 BLA # N/A	NDA Supplement # N/A BLA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A
Proprietary Name: Kyprolis Established/Proper Name: Carfilzomib, 60 mg Dosage Form: Lyophilized powder for injection		Applicant: Onyx Pharmaceuticals, Inc. Agent for Applicant (if applicable): N/A
RPM: Karen Bengtson		Division: Division of Hematology Products
<p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)    <input type="checkbox"/> 505(b)(2)  Efficacy Supplement:    <input type="checkbox"/> 505(b)(1)    <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug.  <input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> This application relies on (explain)</p> <p><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes    <input type="checkbox"/> Updated    Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p>
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>July 27, 2012</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> None

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____	<input checked="" type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  Chemical classification (new NDAs only):</p> <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <input checked="" type="checkbox"/> Fast Track  <input checked="" type="checkbox"/> Rolling Review  <input checked="" type="checkbox"/> Orphan drug designation </div> <div style="width: 45%;"> <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Direct-to-OTC </div> </div> <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> NDAs: Subpart H  <input checked="" type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)  Subpart I  <input type="checkbox"/> Approval based on animal studies   <input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request </div> <div style="width: 45%;"> BLAs: Subpart E  <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)  Subpart H  <input type="checkbox"/> Approval based on animal studies   REMS: <input type="checkbox"/> MedGuide  <input type="checkbox"/> Communication Plan  <input type="checkbox"/> ETASU  <input type="checkbox"/> MedGuide w/o REMS  <input checked="" type="checkbox"/> REMS not required </div> </div> <p>Comments:</p>	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action (by OEP)</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other Burst

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.



❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

☐ Yes ☐ No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

*If "Yes," skip to question (4) below. If "No," continue with question (2).*

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

☐ Yes ☐ No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

*If "No," continue with question (3).*

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

☐ Yes ☐ No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).*

*If "No," continue with question (5).*

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<b>CONTENTS OF ACTION PACKAGE</b>	
❖ Copy of this Action Package Checklist <sup>4</sup>	July 24, 2012
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) July 20, 2012
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	July 17, 2012
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	September 27, 2011
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	Velcade (January 23, 2012)

<sup>4</sup> Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	N/A
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	N/A
<ul style="list-style-type: none"> <li>Example of class labeling, if applicable</li> </ul>	N/A
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	Container - 5/22/12 Carton - 5/14/12
❖ Proprietary Name <ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>Review(s) (<i>indicate date(s)</i>)</li> <li>Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</li> </ul>	June 22, 2012 (final review) 12/15/11 (conditionally acceptable), 12/08/11 (initial review)
❖ Labeling reviews ( <i>indicate dates of reviews and meetings</i> )	<input checked="" type="checkbox"/> RPM 12/7/11 <input checked="" type="checkbox"/> DMEPA 6/12/12; 2/3/12 <input type="checkbox"/> DMPP/PLT (DRISK) N/A <input checked="" type="checkbox"/> ODPD (DDMAC) 5/25/12 (PI); 5/10/12 (carton/container) <input type="checkbox"/> SEALD N/A <input type="checkbox"/> CSS N/A <input checked="" type="checkbox"/> Other reviews 5/10/12 Pediatrics (PMHS)
<b>Administrative / Regulatory Documents</b>	
❖ Administrative Reviews ( <i>e.g., RPM Filing Review<sup>5</sup>/Memo of Filing Meeting</i> ) ( <i>indicate date of each review</i> )	11/22/11
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment ( <i>indicate date</i> )	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>This application is on the AIP               <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action

<sup>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Pediatrics ( <i>approvals only</i> )	
<ul style="list-style-type: none"> <li>Date reviewed by PeRC <u>N/A</u> If PeRC review not necessary, explain: <u>Carfilzomib has orphan designation for the indication of multiple myeloma</u></li> <li>Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul>	<input type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent ( <i>include certification</i> )	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications ( <i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i> )	7/17/12; 7/13/12 (2); 7/11/12 (2); 7/10/12; 7/3/12; 6/29/12; 6/26/12; 6/22/12; 6/13/12; 6/8/12 (2); 5/18/12; 5/16/12; 5/11/12; 4/27/12; 4/12/12; 4/10/12; 4/3/12; 3/29/12; 3/27/12; 2/16/12; 2/13/12; 2/3/12; 1/20/12; 1/10/12; 1/3/12; 12/22/11; 12/21/11; 12/8/11(2); 11/29/11; 11/28/11 (2); 11/21/11; 11/14/11 (2); 10/18/11; 10/6/11; 10/5/11
❖ Internal memoranda, telecons, etc.	11/4/11; 10/19/11
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>Regulatory Briefing (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg 9/28/10 (CMC); 8/5/10
<ul style="list-style-type: none"> <li>EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg 8/3/09 (CMC); 11/6/08
<ul style="list-style-type: none"> <li>Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)</li> </ul>	3/30/09 Pre-SPA meeting
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul>	June 20, 2012
<ul style="list-style-type: none"> <li>48-hour alert or minutes, if available (<i>do not include transcript</i>)</li> </ul>	Included
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 7/20/12
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 7/20/12
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 7/24/12 (memo) 7/18/12 (amended); 6/18/12
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None 7/19/12
<b>Clinical Information<sup>6</sup></b>	
❖ Clinical Reviews	
<ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	See clinical review
<ul style="list-style-type: none"> <li>Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	6/19/12
<ul style="list-style-type: none"> <li>Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None

<sup>6</sup> Filing reviews should be filed with the discipline reviews.



❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	6/19/12 (pg 17 Clinical Review)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None 12/19/11 (DCRP)
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	N/A N/A <input type="checkbox"/> None 7/13/12
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input type="checkbox"/> None requested Summary: 4/13/12 Letters: 4/9/12; 4/5/12; 4/5/12; 4/5/12
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None See Statistical Review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None See Statistical Review
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 5/31/12; 11/2/11 (filing)
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None See Clin Pharm Review
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 6/6/12; 6/14/12 (filing) 3/7/12 (QT-IRT Consult Review)
❖ DSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 6/7/12
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 6/6/12
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 6/29/12 (amendment); 6/1/12; 11/4/11 (filing)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 6/7/12
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None See Products Quality DP and DS Reviews
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 5/29/12 (DS); 6/29/12 (amendment to DP) 5/25/12 (DP); 5/24/12 (Biopharm) 11/10/11 (filing CMC); 11/9/11 (filing - biopharm)
❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not needed 5/8/12; 11/4/11 (filing)
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input type="checkbox"/> None 1/31/12 (Stats review)
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	5/25/12 (pg 78,79 of Product Quality DP Review)
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	N/A
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	N/A
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>7</sup>)</i>	Date completed: 5/24/12 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>7</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

## Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication **AND** a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.



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/s/  
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KAREN E BENGTSON  
07/24/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** July 24, 2012

**TO:** NDA 202714 File

**FROM:** Albert Deisseroth, M.D., Ph.D.

**SUBJECT:** Corrections to Pharmacology/Toxicology Section of the CDTL Report

**APPLICATION/DRUG:** NDA 202714 – Kyprolis (carfilzomib) for Injection

I was advised that the Pharmacology/Toxicology Review Division has revised their report excerpts of which appear in Section 4 of the CDTL report. I have listed below the revisions implemented Pharmacology/Toxicology review and the locations in the Deisseroth review in which these Pharmacology/Toxicology revisions should apply:

- a. Delete strikeout text; add underlined text in paragraph 3, line 3 of Deisseroth CDTL review: “Embryo-lethality occurred at doses equivalent to or below human exposures ~~doses~~ based on findings of increased pre-implantation loss and post-implantation loss from early resorptions in ~~rats and~~ rabbits.”
- b. Delete strikeout text; add underlined text in paragraph 3, line 1 of Deisseroth CDTL review: “Carfilzomib caused no overt teratogenicity in pregnant rats at ~~exposures (AUC)~~ or ~~in~~ rabbits at doses that were lower than in patients receiving the recommended dose. Embryo-lethality occurred below human ~~exposures or~~ doses based on findings of increased pre-implantation loss and post-implantation loss from early resorptions in ~~rats and~~ rabbits. The negative effects on implantation ~~in both species~~, and fetal weight decreases in rabbits may be secondary due to maternal toxicities, such as body weight and feed consumption decreases.”

Albert Deisseroth, MD, PhD, July 24, 2012

## Bengtson, Karen

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**From:** Bengtson, Karen  
**Sent:** Tuesday, July 17, 2012 4:43 PM  
**To:** Alison Cole  
**Cc:** Karen Meier  
**Subject:** NDA 202714 Carfilzomib Package Insert

**Importance:** High

**Attachments:** cfz-draft-package-insert (17Jul2012).doc

Dear Alison,

Upon review of the draft carfilzomib PI submitted by Onyx on July 16, 2012, there were some additional items discovered. Please see the attached file which shows these revisions in tracked changes and submit updated labeling to the NDA as soon as possible.



cfz-draft-package-i  
nser (17Ju...

If you have any questions, feel free to contact me.

Kind regards,  
Karen

**KAREN BENGTSON**  
Regulatory Project Manager  
Division of Hematology Products  
OHOP/CDER/FDA  
WO22, Room 2189  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
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/s/  
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KAREN E BENGTSON  
07/17/2012

## Bengtson, Karen

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**From:** Bengtson, Karen  
**Sent:** Friday, July 13, 2012 4:14 PM  
**To:** Alison Cole  
**Cc:** Karen Meier  
**Subject:** NDA 202714 Carfilzomib - Package Insert

**Importance:** High

**Attachments:** cfz-draft-package-insert-(13Jul2012).doc

Dear Alison,

Onyx's proposed revisions to the package insert as provided via e-mail on July 13, 2012 are acceptable. However, as we discussed on the phone, please correct the location of the listed patent numbers as shown in the attached file (i.e., place them after the manufacturer's information) before submitting to the NDA.

Please acknowledge receipt of this correspondence.

Kind regards,  
Karen



cfz-draft-package-i  
nser-(13Ju...

### KAREN BENGTON

Regulatory Project Manager  
Division of Hematology Products  
OHOP/CDER/FDA  
WO22, Room 2189  
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/s/  
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KAREN E BENGTSON  
07/16/2012

**Bengtson, Karen**

---

**From:** Bengtson, Karen  
**Sent:** Friday, July 13, 2012 2:30 PM  
**To:** 'Ruben Sanchez'; Leaman, Diane V  
**Cc:** Sunita Zalani; Alison Cole  
**Subject:** RE: NDA 202714 Carfilzomib - PMRs  
**Importance:** High

Dear Ruben,

The revisions you proposed below are acceptable. Please note our further revision shown in green. If there are no further comments, please officially submit the revised PMRs to the NDA with your agreement to perform them as described.

PMR Conduct one or more clinical trials including Phase 3 Protocol 2011-003, supplemented as needed by an additional trial, to evaluate the PK, safety, and efficacy of carfilzomib in patients with varying degrees of renal impairment and those on chronic dialysis following the administration of carfilzomib when given as a 30 minute intravenous infusion at a sufficient dose level that will likely produce comparable exposure and clinical response to those patients without renal impairment who receive carfilzomib doses of 20/56 mg/m<sup>2</sup> using the 30 minute infusion as planned in your upcoming Phase 3 trial Protocol number 2011-003. Collect PK samples following carfilzomib doses of 56 mg/m<sup>2</sup> or highest clinical dose in the protocol. Submit your protocol for Agency review and concurrence prior to initiation.

Please acknowledge receipt of this e-mail.

Kind regards,  
Karen

**KAREN BENGTON**

Regulatory Project Manager  
DHP/OHOP/CDER/FDA  
WO22, Room 2189  
Phone: 301-796-3338  
Fax: 301-796-9845  
E-mail: karen.bengtson@fda.hhs.gov

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**From:** Ruben Sanchez [mailto:rsanchez@onyx.com]  
**Sent:** Thursday, July 12, 2012 7:04 PM  
**To:** Leaman, Diane V; Bengtson, Karen  
**Cc:** Sunita Zalani; Alison Cole  
**Subject:** RE: NDA 202714 Carfilzomib - July 6 PI Resonse

Hi Karen / Diane,

Onyx has completed review of the PMRs provided on by Diane on July 11, 2012. With the exception of PMR #6 (renal impairment study) and as discussed during our teleconference with FDA held on July 11th, Onyx agrees with the proposed PMR language. For PMR #6 and as discussed during the teleconference, Onyx is providing

additional text in **red font** to further clarify the proposed requirement. In addition, the timing has been adjusted to be consistent with Protocol 2011-003.

PMR Conduct **one or more** clinical trials **including Phase 3 Protocol 2011-003, supplemented as needed by an additional trial**, to evaluate the PK, safety, and efficacy of carfilzomib in patients with varying degrees of renal impairment following the administration of carfilzomib when given as a 30 minute intravenous infusion at a sufficient dose level that will likely produce comparable exposure and clinical response to those patients without renal impairment who receive carfilzomib doses of 20/56 mg/m<sup>2</sup> using the 30 minute infusion as planned in your upcoming Phase 3 trial Protocol number 2011-003. Collect PK samples following carfilzomib doses of 56 mg/m<sup>2</sup> or highest clinical dose in the protocol. Submit your protocol for Agency review and concurrence prior to initiation.

PMR Timetable:

Final Protocol Submission: March 2013

Trial Completion: ~~June 2014~~ **December 2015**

Final Report Submission: ~~December 2014~~ **May 2016**

If you have any questions or require further information from Onyx regarding this PMR please do not hesitate to contact Alison or myself.

Regards,  
Ruben

---

**From:** Leaman, Diane V [<mailto:Diane.Leaman@fda.hhs.gov>]

**Sent:** Wednesday, July 11, 2012 5:53 AM

**To:** Alison Cole

**Cc:** Karen Meier; Sunita Zalani; Bengtson, Karen

**Subject:** FW: NDA 202714 Carfilzomib - July 6 PI Resonse

Alison, Karen and Sunita,

I am sending this for Karen Bengtson. Please note the revised wording for the Kyprolis (carfilzomib) for Injection PMRs to be discussed at the teleconference schedule for today (July 11, 2012) at 4:00 PM EDT. The changes are intended to clarify the descriptions.

For Accelerated Approval:

PMR Conduct a randomized controlled trial per Protocol PX-171-009, as finalized, to compare carfilzomib-lenalidomide dexamethasone with lenalidomide dexamethasone in a population of patients with myeloma, whose disease has relapsed after previous response to at least one but not more than three prior therapies, to assess efficacy and safety. Patients' disease is required to show evidence of progression after prior therapy. The trial includes 792 patients. The randomization will balance known important prognostic factors. The goal of the trial is to evaluate the primary endpoint of progression-free survival (PFS) for the carfilzomib-containing arm, as determined by an independent review committee blinded to the treatment given.

PMR Timetable:

Final Protocol Submission: January 2010

Trial Completion: December 2013



Final Report Submission: June 2014

For Postmarketing Requirements under 505(o)

**PMR** Conduct a randomized clinical trial in patients receiving carfilzomib to identify and characterize the cardiac toxicities associated with carfilzomib. You have agreed to conduct this trial as a cardiac sub-trial within your ongoing Protocol 2011-003 (ENDEAVOR). The primary objective is to compare changes in cardiac function between the group receiving carfilzomib and a control group not receiving carfilzomib in a parallel group trial.

The main trial protocol (2011-003) must require a baseline resting ECG and transthoracic ECHO to assess left ventricular (LV) function on all patients. If transthoracic ECHO is not available at some sites, MUGA will be acceptable for baseline screening LVEF evaluation. For the cardiac sub-trial, a subset of patients from the main trial will be assessed for LV and right ventricular (RV) function with transthoracic ECHO (or MUGA for those sites using MUGA at baseline) periodically throughout trial treatment and at the time of the End-of-Treatment visit, using similar test procedures and equipment to allow serial intra-patient comparisons. This cardiac sub-trial must include a minimum of 100 patients and a maximum of 300 patients total (50 to 150 patients per treatment arm). Specific details regarding the interpretation of LVEF changes must be pre-specified and outlined in the SAP for this cardiac toxicity trial. For the sub-trial, readers of the ECHOs/MUGAs must be blinded to the protocol treatment given.

In addition, any patient in the main trial who has a cardiac adverse event (AE) that is considered a clinically significant AE must have an ECHO performed to assess LV and RV function as part of the evaluation of that AE.

Submit a complete cardiac sub-trial protocol for review and concurrence before commencing the sub-trial.

**PMR Timetable:**

2011-003 (ENDEAVOR) Phase 3 cardiac sub-trial

Final sub-trial Protocol Submission: January 2013

Trial Completion: November 2015

Final Report Submission: May 2016

**PMR** Conduct a randomized clinical trial in patients receiving carfilzomib to identify and characterize the pulmonary toxicities associated with carfilzomib. The primary objective is to compare pulmonary toxicities between the group receiving carfilzomib and a control group not receiving carfilzomib in a parallel group trial. You have agreed to conduct this pulmonary sub-trial within your ongoing Protocol 2011-003. On all patients enrolled in the main trial, 2011-003, during screening, obtain a baseline transthoracic ECHO to estimate the pulmonary artery pressures and to assess right ventricular size, thickness, and function, and to serve as the baseline ECHO for later comparisons on all patients. In the pulmonary sub-trial, among a minimum of 100 patients and a maximum of 300 patients total (50 to 150 patients per treatment arm), assess this sub-group periodically for pulmonary artery pressures and right ventricular function with repeat transthoracic ECHO throughout trial treatment and at the time of the End-of-Treatment visit, using similar test procedures and equipment to allow serial intra-patient comparisons. Emergent pulmonary toxicities must be further characterized in all patients receiving carfilzomib in the main trial also, to include at least the following: time course of onset and resolution,

oximetry and/or blood gases, and consultation with a pulmonary specialist, when clinically appropriate, to provide further documentation of the nature of the emergent condition. Document the response to oxygen supplementation and other treatment measures. For the sub-trial, readers of the ECHOs/MUGAs must be blinded to the treatment given.

In the pulmonary sub-trial protocol, pre-specify how comparisons will be performed for changes between the two groups for outcomes related to pulmonary hypertension, right ventricular function, and clinical pulmonary safety events. Additionally, for all patients enrolled in the main trial, any patient who has a cardiac or pulmonary AE that is considered a clinically significant AE must have a follow-up ECHO at the time of the event to assess LV, RV, and pulmonary artery function. Submit a complete pulmonary sub-trial protocol for review and concurrence before commencing the sub-trial.

PMR Timetable:

2011-003 (ENDEAVOR) Phase 3 pulmonary sub-trial

Final sub-trial Protocol Submission: January 2013  
 Trial Completion: November 2015  
 Final Report Submission: May 2016

PMR Conduct a clinical trial (2011-003 ENDEAVOR) to evaluate the safety of a 30-minute intravenous infusion of carfilzomib at the dose of 20/56 mg/m<sup>2</sup> in patients with multiple myeloma.

PMR Timetable:

2011-003 (ENDEAVOR) Phase 3 Trial

Final Protocol Submission: March 2012  
 Trial Completion: November 2015  
 Final Report Submission: May 2016

PMR Conduct a clinical trial (PX-171-007) to evaluate the safety of a 30-minute intravenous infusion of carfilzomib at the dose of 20/56 mg/m<sup>2</sup> in patients with multiple myeloma

PMR Timetable:

PX-171-007 Phase 2 Trial

Final Protocol Submission: August 2007  
 Trial Completion: June 2014  
 Final Report Submission: December 2014

PMR Conduct a clinical trial in patients with hepatic impairment to assess safety and PK characteristics of carfilzomib administered as a 30-minute infusion. The number of patients enrolled in the trial should be sufficient to detect PK differences that would warrant dosage adjustment recommendations in the labeling. The duration of the trial should be sufficient (several cycles) to reasonably characterize potential safety issues. The PK sampling scheme should be optimized to accurately estimate relevant PK parameters for the parent drug. A data analysis plan must be included in the protocol. Submit your protocol for Agency review and concurrence prior to initiation.

## PMR Timetable:

Final Protocol Submission: March 2013  
Trial Completion: December 2015  
Final Report Submission: May 2016

PMR Conduct a clinical trial to evaluate the PK, safety, and efficacy of carfilzomib in patients with varying degrees of renal impairment following the administration of carfilzomib when given as a 30-minute intravenous infusion at a sufficient dose level that will likely produce comparable exposure and clinical response to those patients without renal impairment who receive carfilzomib doses of 20/56 mg/m<sup>2</sup> using the 30-minute infusion as planned in your upcoming Phase 3 trial Protocol number 2011-003. Collect PK samples following carfilzomib doses of 56 mg/m<sup>2</sup> or highest clinical dose in the protocol. Submit your protocol for Agency review and concurrence prior to initiation.

## PMR Timetable:

Final Protocol Submission: March 2013  
Trial Completion: June 2014  
Final Report Submission: December 2014

Sincerely,

Diane Leaman, SRPM  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-1424.

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/s/  
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KAREN E BENGTSON  
07/13/2012

## Bengtson, Karen

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**From:** Bengtson, Karen  
**Sent:** Wednesday, July 11, 2012 2:01 PM  
**To:** 'Alison Cole'  
**Subject:** NDA 202714 - Carfilzomib PI

**Importance:** High

**Attachments:** cfz-draft-package-insert-11jul2012.doc

Dear Alison,

We have made two adjustments to the labeling sent to you yesterday, July 10, 2012. The first is to the Medwatch statement in the Highlights section and the second is to Subsection 6.1 "Clinical Trials Safety Experience." Please use this version for discussion at today teleconference and going forward.

Thank you,  
Karen



cfz-draft-package-i  
nser-11jul...

**KAREN BENGTON**  
Regulatory Project Manager  
Division of Hematology Products  
OHOP/CDER/FDA  
WO22, Room 2189  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
Phone: 301-796-3338  
Fax: 301-796-9845  
E-mail: karen.bengtson@fda.hhs.gov

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/s/  
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KAREN E BENGTSON  
07/11/2012

## Bengtson, Karen

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**From:** Leaman, Diane V  
**Sent:** Wednesday, July 11, 2012 8:53 AM  
**To:** acole@onyx-pharm.com  
**Cc:** kmeier@onyx-pharm.com; szalani@onyx-pharm.com; Bengtson, Karen  
**Subject:** FW: NDA 202714 Carfilzomib - July 6 PI Resonse

Alison, Karen and Sunita,

I am sending this for Karen Bengtson. Please note the revised wording for the Kyprolis (carfilzomib) for Injection PMRs to be discussed at the teleconference schedule for today (July 11, 2012) at 4:00 PM EDT. The changes are intended to clarify the descriptions.

### For Accelerated Approval:

**PMR** Conduct a randomized controlled trial per Protocol PX-171-009, as finalized, to compare carfilzomib-lenalidomide dexamethasone with lenalidomide dexamethasone in a population of patients with myeloma, whose disease has relapsed after previous response to at least one but not more than three prior therapies, to assess efficacy and safety. Patients' disease is required to show evidence of progression after prior therapy. The trial includes 792 patients. The randomization will balance known important prognostic factors. The goal of the trial is to evaluate the primary endpoint of progression-free survival (PFS) for the carfilzomib-containing arm, as determined by an independent review committee blinded to the treatment given.

#### PMR Timetable:

Final Protocol Submission: January 2010  
Trial Completion: December 2013  
Final Report Submission: June 2014

### For Postmarketing Requirements under 505(o)

**PMR** Conduct a randomized clinical trial in patients receiving carfilzomib to identify and characterize the cardiac toxicities associated with carfilzomib. You have agreed to conduct this trial as a cardiac sub-trial within your ongoing Protocol 2011-003 (ENDEAVOR). The primary objective is to compare changes in cardiac function between the group receiving carfilzomib and a control group not receiving carfilzomib in a parallel group trial.

The main trial protocol (2011-003) must require a baseline resting ECG and transthoracic ECHO to assess left ventricular (LV) function on all patients. If transthoracic ECHO is not available at some sites, MUGA will be acceptable for baseline screening LVEF evaluation. For the cardiac sub-trial, a subset of patients from the main trial will be assessed for LV and right ventricular (RV) function with transthoracic ECHO (or MUGA for those sites using MUGA at baseline) periodically throughout trial treatment and at the time of the End-of-Treatment visit, using similar test procedures and equipment to allow serial intra-patient comparisons. This cardiac sub-trial must include a minimum of 100 patients and a maximum of 300 patients total (50 to 150 patients per treatment arm). Specific details regarding the interpretation of LVEF changes

must be pre-specified and outlined in the SAP for this cardiac toxicity trial. For the sub-trial, readers of the ECHOs/MUGAs must be blinded to the protocol treatment given.

In addition, any patient in the main trial who has a cardiac adverse event (AE) that is considered a clinically significant AE must have an ECHO performed to assess LV and RV function as part of the evaluation of that AE.

Submit a complete cardiac sub-trial protocol for review and concurrence before commencing the sub-trial.

PMR Timetable:

2011-003 (ENDEAVOR) Phase 3 cardiac sub-trial

Final sub-trial Protocol Submission: January 2013

Trial Completion: November 2015

Final Report Submission: May 2016

PMR Conduct a randomized clinical trial in patients receiving carfilzomib to identify and characterize the pulmonary toxicities associated with carfilzomib. The primary objective is to compare pulmonary toxicities between the group receiving carfilzomib and a control group not receiving carfilzomib in a parallel group trial. You have agreed to conduct this pulmonary sub-trial within your ongoing Protocol 2011-003. On all patients enrolled in the main trial, 2011-003, during screening, obtain a baseline transthoracic ECHO to estimate the pulmonary artery pressures and to assess right ventricular size, thickness, and function, and to serve as the baseline ECHO for later comparisons on all patients. In the pulmonary sub-trial, among a minimum of 100 patients and a maximum of 300 patients total (50 to 150 patients per treatment arm), assess this sub-group periodically for pulmonary artery pressures and right ventricular function with repeat transthoracic ECHO throughout trial treatment and at the time of the End-of-Treatment visit, using similar test procedures and equipment to allow serial intra-patient comparisons. Emergent pulmonary toxicities must be further characterized in all patients receiving carfilzomib in the main trial also, to include at least the following: time course of onset and resolution, oximetry and/or blood gases, and consultation with a pulmonary specialist, when clinically appropriate, to provide further documentation of the nature of the emergent condition. Document the response to oxygen supplementation and other treatment measures. For the sub-trial, readers of the ECHOs/MUGAs must be blinded to the treatment given.

In the pulmonary sub-trial protocol, pre-specify how comparisons will be performed for changes between the two groups for outcomes related to pulmonary hypertension, right ventricular function, and clinical pulmonary safety events. Additionally, for all patients enrolled in the main trial, any patient who has a cardiac or pulmonary AE that is considered a clinically significant AE must have a follow-up ECHO at the time of the event to assess LV, RV, and pulmonary artery function. Submit a complete pulmonary sub-trial protocol for review and concurrence before commencing the sub-trial.

PMR Timetable:

2011-003 (ENDEAVOR) Phase 3 pulmonary sub-trial

Final sub-trial Protocol Submission: January 2013

Trial Completion: November 2015

Final Report Submission: May 2016



PMR Conduct a clinical trial (2011-003 ENDEAVOR) to evaluate the safety of a 30-minute intravenous infusion of carfilzomib at the dose of 20/56 mg/m<sup>2</sup> in patients with multiple myeloma.

PMR Timetable:

2011-003 (ENDEAVOR) Phase 3 Trial

Final Protocol Submission: March 2012  
Trial Completion: November 2015  
Final Report Submission: May 2016

PMR Conduct a clinical trial (PX-171-007) to evaluate the safety of a 30-minute intravenous infusion of carfilzomib at the dose of 20/56 mg/m<sup>2</sup> in patients with multiple myeloma

PMR Timetable:

PX-171-007 Phase 2 Trial

Final Protocol Submission: August 2007  
Trial Completion: June 2014  
Final Report Submission: December 2014

PMR Conduct a clinical trial in patients with hepatic impairment to assess safety and PK characteristics of carfilzomib administered as a 30 minute infusion. The number of patients enrolled in the trial should be sufficient to detect PK differences that would warrant dosage adjustment recommendations in the labeling. The duration of the trial should be sufficient (several cycles) to reasonably characterize potential safety issues. The PK sampling scheme should be optimized to accurately estimate relevant PK parameters for the parent drug. A data analysis plan must be included in the protocol. Submit your protocol for Agency review and concurrence prior to initiation.

PMR Timetable:

Final Protocol Submission: March 2013  
Trial Completion: December 2015  
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PMR Conduct a clinical trial to evaluate the PK, safety, and efficacy of carfilzomib in patients with varying degrees of renal impairment following the administration of carfilzomib when given as a 30 minute intravenous infusion at a sufficient dose level that will likely produce comparable exposure and clinical response to those patients without renal impairment who receive carfilzomib doses of 20/56 mg/m<sup>2</sup> using the 30 minute infusion as planned in your upcoming Phase 3 trial Protocol number 2011-003. Collect PK samples following carfilzomib doses of 56 mg/m<sup>2</sup> or highest clinical dose in the protocol. Submit your protocol for Agency review and

concurrence prior to initiation.

PMR Timetable:  
Final Protocol Submission: March 2013  
Trial Completion: June 2014  
Final Report Submission: December 2014

Sincerely,

Diane Leaman, SRPM  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-1424.

---

**From:** Bengtson, Karen  
**Sent:** Tuesday, July 10, 2012 10:12 AM  
**To:** 'Alison Cole'  
**Cc:** Karen Meier; Sunita Zalani  
**Subject:** RE: NDA 202714 Carfilzomib - July 6 PI Resonse

Dear Alison,

I would like to confirm whether your team will be available for a brief teleconference this Wednesday, July 11, 2012 from 3:30-4:00 PM (ET) to discuss labeling and PMRs. There were some minor adjustments needed to the text of some of the PMRs. This will require resubmission of the PMRs with your agreement. We plan to cover those updates in the meeting as well.

Thank you,  
Karen

**KAREN BENGTON**  
Regulatory Project Manager  
DHP/OHOP/CDER/FDA  
WO22, Room 2189  
Phone: 301-796-3338  
Fax: 301-796-9845  
E-mail: karen.bengtson@fda.hhs.gov

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**From:** Alison Cole [mailto:acole@onyx.com]  
**Sent:** Friday, July 06, 2012 4:48 PM  
**To:** Bengtson, Karen  
**Cc:** Karen Meier; Sunita Zalani

**Subject:** NDA 202714 Carfilzomib - July 6 PI Resonse

Dear Karen,

Please find attached Onyx's response to FDA's July 3<sup>rd</sup> PI comments. We can be available to have a brief telecon to discuss the indication or any other elements of the response if FDA deems it appropriate. There may be some minor QC updates that we catch over the next several days. I will keep you posted.

Kind Regards,  
Alison

**Alison T. Cole**  
Senior Director | Regulatory Affairs  
Onyx Pharmaceuticals, Inc. | 249 E. Grand Ave., | South San Francisco | CA 94080  
direct: 650.266.1672  
cell: 510.289.8523  
[acole@onyx-pharm.com](mailto:acole@onyx-pharm.com)

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/s/  
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DIANE V LEAMAN

07/11/2012

**Bengtson, Karen**

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**From:** Bengtson, Karen  
**Sent:** Tuesday, July 10, 2012 5:06 PM  
**To:** 'Alison Cole'  
**Cc:** Karen Meier; Sunita Zalani  
**Subject:** RE: NDA 202714 Carfilzomib - FDA Response Onyx's July 6, 2012 Revisions  
**Importance:** High  
**Attachments:** cfz-draft-package-insert-10jul2012.doc

Dear Alison,

Please find attached the FDA's responses to Onyx's July 6, 2012 comments and revisions to the Carfilzomib PI in preparation for our teleconference tomorrow, July 11, 2012 at 3:30 - 4:00 PM.

Kind regards,  
Karen

**KAREN BENGTSON**

Regulatory Project Manager  
 DHP/OHOP/CDER/FDA  
 WO22, Room 2189  
 Phone: 301-796-3338  
 Fax: 301-796-9845  
 E-mail: karen.bengtson@fda.hhs.gov

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**From:** Alison Cole [mailto:acole@onyx.com]  
**Sent:** Friday, July 06, 2012 4:48 PM  
**To:** Bengtson, Karen  
**Cc:** Karen Meier; Sunita Zalani  
**Subject:** NDA 202714 Carfilzomib - July 6 PI Resonse

Dear Karen,

Please find attached Onyx's response to FDA's July 3<sup>rd</sup> PI comments. We can be available to have a brief telecon to discuss the indication or any other elements of the response if FDA deems it appropriate. There may be some minor QC updates that we catch over the next several days. I will keep you posted.

Kind Regards,  
Alison

**Alison T. Cole**

Senior Director | Regulatory Affairs  
 Onyx Pharmaceuticals, Inc. | 249 E. Grand Ave., | South San Francisco | CA 94080  
 direct: 650.266.1672  
 cell: 510.289.8523  
[acole@onyx-pharm.com](mailto:acole@onyx-pharm.com)

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KAREN E BENGTSON  
07/11/2012

**Bengtson, Karen**

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**From:** Bengtson, Karen  
**Sent:** Tuesday, July 03, 2012 11:27 AM  
**To:** 'Alison Cole'  
**Cc:** Karen Meier; Sunita Zalani  
**Subject:** RE: NDA 202714 Carfilzomib - Draft Package Insert Response  
**Importance:** High  
**Attachments:** cfz-draft-package-insert-3July2012.doc

Dear Alison,

Attached is the Carfilzomib package insert (PI) for NDA 202714 in response to your comments/revisions provided via e-mail on June 27, 2012. . We request that you respond by Friday, July 6, 2012.

Where Onyx agrees with the labeling, please accept the tracked changes. Where Onyx does not agree with the labeling revisions, please provide your comments and proposed language (shown in tracked-changes). Again, please check the document for formatting.

Kind regards,

Karen

**KAREN BENGTSON**

Regulatory Project Manager  
DHP/OHOP/CDER/FDA  
WO22, Room 2189  
Phone: 301-796-3338  
Fax: 301-796-9845  
E-mail: karen.bengtson@fda.hhs.gov

---

**From:** Alison Cole [mailto:acole@onyx.com]  
**Sent:** Wednesday, June 27, 2012 7:46 PM  
**To:** Bengtson, Karen  
**Cc:** Karen Meier; Sunita Zalani  
**Subject:** NDA 202714 Carfilzomib - Draft Package Insert Response

Dear Karen,

Attached is Onyx's response to the FDA PI revisions received on June 22, 2012. As requested, we have accepted track changes where we agreed with FDA and have provided comments and proposed language in track changes mode. We have also reviewed the document for formatting, spacing and margins.

If you have any questions, please feel free to contact me.

Kind Regards,  
Alison

**Alison T. Cole**

Senior Director | Regulatory Affairs

Onyx Pharmaceuticals, Inc. | 249 E. Grand Ave., | South San Francisco | CA 94080

direct: 650.266.1672

cell: 510.289.8523

[acole@onyx-pharm.com](mailto:acole@onyx-pharm.com)

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KAREN E BENGTSON  
07/05/2012

## Bengtson, Karen

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**From:** Bengtson, Karen  
**Sent:** Friday, June 29, 2012 4:44 PM  
**To:** 'Alison Cole'  
**Cc:** Ruben Sanchez  
**Subject:** RE: NDA 202714 Carfilzomib - Onyx PMR Responses 6/28/12  
**Importance:** High

Dear Alison,

Please official submit this to the NDA with a statement that you agree to perform the PMRs as described.

Kind regards,  
Karen

### KAREN BENGTSON

Regulatory Project Manager  
DHP/OHOP/CDER/FDA  
WO22, Room 2189  
Phone: 301-796-3338  
Fax: 301-796-9845  
E-mail: karen.bengtson@fda.hhs.gov

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**From:** Alison Cole [mailto:[acole@onyx.com](mailto:acole@onyx.com)]  
**Sent:** Thursday, June 28, 2012 7:36 PM  
**To:** Bengtson, Karen  
**Cc:** Ruben Sanchez  
**Subject:** NDA 202714 Carfilzomib - Onyx PMR Responses 6/28/12

Dear Karen,

I have attached Onyx's responses to the FDA's PMR comments from 6/26/12. Please let me know if you have any questions.

Kind Regards,  
Alison

### Alison T. Cole

Senior Director | Regulatory Affairs  
Onyx Pharmaceuticals, Inc. | 249 E. Grand Ave., | South San Francisco | CA 94080  
direct: 650.266.1672  
cell: 510.289.8523  
[acole@onyx-pharm.com](mailto:acole@onyx-pharm.com)

## Summary of Post-Marketing Requirements (PMR) for Carfilzomib with Timelines

### PMRs under Accelerated Approval (Subpart H)

#### **PMR 1: Requirement under Subpart H to Verify Clinical Benefit**

To verify and describe the clinical benefit of carfilzomib, you agree to conduct one or more randomized controlled trials.

You agree to conduct a randomized controlled trial per Protocol ~~PX-171-0092011-003~~, as finalized, to compare carfilzomib-lenalidomide dexamethasone with lenalidomide ~~bortezomib~~-dexamethasone in a population of patients with myeloma, whose disease has relapsed after previous response to at least one but not more than three prior therapies, to assess efficacy and safety. Patients are required to show evidence of progression after prior therapy. ~~Estimated sample size is~~ The trial includes 792 patients. 900- The randomization will balance known important prognostic factors. The goal of the trial is to ~~demonstrate clinical and statistical superiority on~~ evaluate the primary endpoint of progression-free survival (PFS) for the carfilzomib-containing arm, as determined by an independent review committee blinded to the treatment given.

In your response, please propose the following PMR Schedule milestones:

#### PX-171-009 (ASPIRE) Phase 3 Study

- a. Final Protocol Submission (01/2010)
- b. Trial Completion (12/2013)
- c. Final Report Submission (06/2014)

**ONYX RESPONSE (6/22/12): Onyx intends to fulfill the requirement under Subpart H to provided confirmation of clinical benefit through completion of the ASPIRE Trial (PX-171-009). This study protocol is being conducted under a Special Protocol Assessment and the PMR schedule milestones are noted above.**

**FDA Response (6/26/12): Accepted.**

**Note to applicant:** The dates have to be in final form (in month/year format) as part of the documentation of an approval action. For all PMRs, provide the dates you consider to be feasible in your reply. Once the dates are set by you, current rules do not allow changes.

**ONYX RESPONSE (6/28/12): Dates have been provided. See proposed edits to study description above.**

### PMRs under FDAAA

#### **PMR 2: Cardiac Safety Trial**

Cardiac dysfunction is common in heavily pretreated multiple myeloma patients. Cardiac dysfunction has been observed with carfilzomib, and the safety of carfilzomib in the relapsed myeloma population is not well characterized.

Therefore, conduct a randomized clinical trial in patients receiving carfilzomib to identify and characterize the cardiac toxicities associated with carfilzomib. We suggest that you consider doing this trial as a sub-study within your proposed Protocol 2011-003, or you may propose a separate trial with this safety objective. The primary objective is to compare changes in cardiac function between the group receiving carfilzomib and a control group not receiving carfilzomib in a parallel group trial.

If you choose to add this sub-study to your proposed protocol, the trial protocol must require a resting ECG and a baseline transthoracic ECHO to assess LVEF on all patients. If transthoracic ECHO is not available at some sites, MUGA will be acceptable for baseline screening LVEF evaluation. A subset of patients from both trial treatment arms should be assessed for LVEF and right ventricular (RV) function with transthoracic ECHO (or MUGA for those sites using MUGA at baseline) periodically throughout study treatment and at the time of the End-of-Treatment visit, using similar test procedures and equipment to allow serial intra-patient comparisons. The subset of patients must include a minimum of 100 patients and a maximum of 300 patients total (50 to 150 patients per treatment arm). Specific details regarding the interpretation of LVEF changes in the subset of patients must be pre-specified and outlined in the SAP for this sub-study. Readers of the ECHOs/MUGAs must be blinded to the treatment given.

In addition, any patient who has a cardiac adverse event (AE) that is considered a clinically significant AE must have an ECHO performed to assess left ventricular (LV) and right ventricular function as part of the evaluation of that AE; this AE evaluation applies to all patients enrolled in the trial.

Submit a complete protocol for review and concurrence before commencing the trial.

In your response, please propose the following PMR Schedule milestones:

2011-003 (ENDEAVOR) Phase 3 Study

- a. Final Protocol Submission (03/2012)
- b. Trial Completion (11/2015)
- c. Final Report Submission (05/2016)

Notes to Applicant:

1. For initial planning, you may indicate the number of months/years that you would consider to be feasible and occurring following an approval date.
2. The term “final protocol submission” means the protocol that has been agreed to by both the FDA and you and is in the final form for initiating the trial.

**ONYX RESPONSE (6/22/12): A cardiac sub-study is currently incorporated into Protocol 2011-003 (ENDEAVOR) as described above, and is designed to evaluate both left and right ventricular function in a subset of patients from both treatment arms in a serial fashion by central review. In addition, Protocol 2011-003 specifies that baseline ECHO's be obtained on all patients, and ii) follow-up ECHO to be obtained on any patient who experiences a clinically significant cardiac adverse event.**

**FDA Response (6/26/12): Accepted, with final dates required.**

**ONYX RESPONSE (6/28/12): Dates have been provided. A cardiac sub-study will be conducted as part of Protocol 2011-003 (ENDEAVOR) as described above. The sub-study will evaluate both left and right ventricular function in a subset of patients from both treatment arms in a serial fashion by central review. Protocol 2011-003 specifies that (i) baseline ECHO's to be obtained on all patients, and ii) follow-up ECHO to be obtained on any patient who experiences a clinically significant cardiac adverse event.**

### **PMR 3: Pulmonary Safety Trial**

Pulmonary toxicities have been observed with carfilzomib, but they are not well characterized.

Therefore, conduct a randomized clinical trial in patients receiving carfilzomib to identify and characterize the pulmonary toxicities associated with carfilzomib. The primary objective is to compare pulmonary toxicities between the group receiving carfilzomib and a control group not receiving carfilzomib in a parallel group trial. This could be done within the proposed Protocol 2011-003 as a sub-study or as a separate trial as you prefer. If performed as a sub-study of protocol 2011-003, obtain this baseline exam on all patients enrolled in that trial, during screening, and to serve as the baseline ECHO for later comparisons on all patients. This study must include a baseline transthoracic ECHO to estimate the pulmonary artery pressures and to assess right ventricular size, thickness, and function. Subsequently, a subset of patients from both treatment arms should be assessed periodically for pulmonary artery pressures and right ventricular function with repeat transthoracic ECHO throughout study treatment and at the time of the End-of-Treatment visit, using similar test procedures and equipment to allow serial intra-patient comparisons. Emergent pulmonary toxicities must be further characterized in all patients receiving carfilzomib, to include at least the following: time course of onset and resolution, oximetry and/or blood gases, and consultation with a pulmonary specialist, when available, to provide further documentation of the nature of the emergent condition. Document the response to oxygen supplementation and other treatment measures.

A minimum of 100 patients and a maximum of 300 patients total are necessary (50 to 150 patients per treatment arm). Pre-specify how comparisons will be performed for changes between the two groups for outcomes related to pulmonary hypertension, right ventricular function, and clinical pulmonary safety events. Additionally, any patient who has a cardiac or pulmonary AE that is considered a clinically significant AE, must have a follow-up ECHO at the time of the event to assess LV, RV, and pulmonary artery function. This AE evaluation is for all patients enrolled in the study.

In your response, please propose the following PMR Schedule milestones:

#### 2011-003 (ENDEAVOR) Phase 3 Study

- a. Final Protocol Submission (03/2012)

- b. Trial Completion (11/2015)
- c. Final Report Submission (05/2016)

**ONYX RESPONSE (6/22/12):** As noted in response to PMR 2, Onyx plans to obtain baseline ECHOs (or MUGA's when ECHO is not available) in all patients enrolled in Protocol 2011-003, and also to perform a sub-study on a subset of patients from each arm to allow serial intra-patient comparisons.

Onyx will develop an additional case report form in order to capture information regarding pulmonary studies performed and their results and will provide guidance to investigators in Protocol 2011-003 regarding recommended evaluations that may be performed in response to a clinically significant pulmonary adverse event. However, Onyx is concerned about mandating additional evaluations in the setting of a Phase 3 trial because of potential negative impact on accrual.

**FDA Response (6/26/12):** Accepted pending the following notes:

- a. The dates have to be in final form as part of the documentation.
- b. If dyspnea leads to the provision of supplemental oxygen, it is standard care as part of providing oxygen to measure systemic oxygen by any of several means, including oximetry. We consider these results important in assessing safety and reasonable to obtain per protocol.

**ONYX RESPONSE (6/28/12):** Onyx agrees and will collect data on systemic oxygen levels in patients who have dyspnea that leads to the provision of supplemental oxygen. Per FDA request, dates have been provided. No further comments.

#### **PMR 4: Study of Carfilzomib Administered as a 30-Minute Infusion**

The proposed dose of carfilzomib submitted as part of NDA 202714 is 20/27 mg/m<sup>2</sup> administered intravenously as a bolus over 2 to 10 min. Conduct a safety study using the 30 minutes intravenous infusion of carfilzomib at the dose of 20/56 mg/m<sup>2</sup> in patients with multiple myeloma.

Conduct your safety evaluation using either of the following two options or propose an alternative option for our review and concurrence:

- Conduct the study as part of the planned Phase 3 trial (Protocol number 2011-003)

OR

- Conduct a stand-alone safety study in patients receiving carfilzomib. Conduct the study for sufficient duration in order to detect and assess safety signals. If you choose to do a stand safety trial, submit a complete study protocol for review and concurrence.

In your response, please propose the following PMR Schedule milestones:

#### 2011-003 (ENDEAVOR) Phase 3 Study

- a. Final Protocol Submission (03/2012)

- b. Study Completion (11/2015)
- c. Final Report Submission (05/2016)

PX-171-007 Phase 2 Study

- a. Final Protocol Submission (08/2007)
- b. Study Completion (06/2014)
- c. Final Report Submission (12/2014)

**ONYX RESPONSE (6/22/12):** The safety assessment of the 30 minute infusion rate is one of the objectives of Protocol 2011-003. The safety will be submitted as part of the clinical study report for the trial. In addition, Onyx has completed the enrollment of 49 patients with multiple myeloma into the Phase 2 PX-171-007 study. This study is designed to evaluate the safety and activity of the 30-minute infusion at 2 dose levels (either 20/45 or the 20/56 mg/m<sup>2</sup>).

**FDA Response (6/26/12):** Accepted. Please indicate that you agree to submit the results of both trials, as they separately become available, for this safety study.

**ONYX RESPONSE (6/28/12):** Onyx agrees to submit the results of both trials as they become available. Dates have been provided. No further comments.

**PK Trials:**

**PMR 5: Hepatic Impairment**

Conduct a clinical trial in patients with hepatic impairment to assess safety and PK characteristics of carfilzomib administered as a 30 minute infusion. The number of patients enrolled in the study should be sufficient to detect PK differences that would warrant dosage adjustment recommendations in the labeling. The duration of the study should be sufficient (several cycles) to reasonably characterize potential safety issues. The PK sampling scheme should be optimal to accurately estimate relevant PK parameters for the parent drug. A data analysis plan must be included in the protocol. Submit your protocol for Agency review and concurrence prior to initiation.

In your response, please propose the following PMR Schedule milestones:

Draft timeline for proposed phase 1 study in patients with hepatic impairment

- a. Final Protocol Submission (3/2013)
- b. Study Completion (12/2015)
- c. Final Report Submission (05/2016)

**ONYX RESPONSE (6/22/12):** Onyx would like to further understand the Agency's concerns regarding administration of carfilzomib to patients with hepatic impairment to ensure the Onyx proposal meets the Agency's objectives. Carfilzomib is rapidly cleared from the plasma compartment with mean clearance values (150–263 L/hr at 20 and 27 mg/m<sup>2</sup>) that are greater than liver blood flow, suggesting that carfilzomib is cleared primarily extrahepatically. In animal studies, less than 1% of carfilzomib was excreted intact in bile. Carfilzomib is rapidly and systemically metabolized. The predominant metabolites in human plasma and urine, and those

generated in vitro by human hepatocytes, are peptide fragments of the parent drug (M14 and M15) and carfilzomib diol (M16), suggesting that peptidase cleavage and epoxide hydrolysis are principal pathways of metabolism. These metabolites are formed immediately after administration and are inactive. In view of these data, no formal study was conducted to assess carfilzomib PK in patients with hepatic impairment.

Onyx would like to request an opportunity to further discuss the applicability of this Post Marketing Request to the current NDA under review.

**FDA Response (6/26/12):** See response under PMR 6

**ONYX RESPONSE (6/28/12):** Onyx agrees to conduct a clinical trial in patients with hepatic impairment to assess the safety and PK characteristics of repeat dose carfilzomib administered as a 30 minute infusion at 20/56 mg/m<sup>2</sup>. We propose to include patients with hematologic and/or solid tumor malignancies. The trial will be conducted in accordance with applicable guidance documents. A draft protocol will be submitted to the Agency for review. Dates have been provided.

#### **PMR 6: Renal Impairment**

Since PK assessment in the renal impairment study was conducted following carfilzomib doses of 15/20 mg/m<sup>2</sup> given intravenously over 2 – 10 minutes and since this dosing regimen may not necessarily produce clinical responses at the level that would be seen with higher doses, evaluate the PK, safety, and efficacy of carfilzomib in patients with varying degrees of renal impairment following the administration of carfilzomib when given as a 30 minute intravenous infusion at a sufficient dose level that will likely produce comparable exposure and clinical response to those patients without renal impairment that receive carfilzomib doses of 20/56 mg/m<sup>2</sup> using the 30 minute infusion as planned in your upcoming Phase 3 trial Protocol number 2011-003. Collect PK samples following carfilzomib doses of 56 mg/m<sup>2</sup> or highest clinical dose in the protocol. Conduct your renal impairment evaluation using either of the following two options or propose an alternative option for our review and concurrence:

- Amend the planned Phase 3 trial (Protocol number 2011-003) to include patients with varying degrees of renal impairment and those on chronic dialysis.

OR

- Conduct a stand-alone renal impairment study in patients with varying degrees of renal impairment including patients with mild, moderate, severe renal function and those on chronic dialysis. Conduct the study for sufficient duration in order to detect and assess safety and efficacy signals. If you choose to do a stand-alone renal impairment trial, submit a complete study protocol for review and concurrence by the Agency.



In your response, please propose the following PMR Schedule milestones:

Draft timeline for proposed phase 1 study in renal impaired patients

- a. Final Protocol Submission (03/2013)
- b. Study Completion (06/2014)
- c. Final Report Submission (12/2014)

**ONYX RESPONSE (6/22/12):** In Study PX-171-005, the sponsor established that the pharmacokinetics (PK) of carfilzomib delivered over 2 – 10 minutes at 15 and 20 mg/m<sup>2</sup> to multiple myeloma patients was not affected by renal status including patients on chronic dialysis. Carfilzomib was well tolerated and active in patients with renal impairment in this study. Therefore, no dose adjustment for patients with renal insufficiency including patients on dialysis is recommended and proposed for the label. Onyx will continue to evaluate the PK, safety and efficacy of carfilzomib in patients with mild renal insufficiency:

- PX-171-009 POP PK analysis will evaluate the effect of creatinine clearance on the plasma clearance of carfilzomib.
- Onyx has completed the enrollment of 49 patients with multiple myeloma into the Phase 2 PX-171-007 study. This study is designed to evaluate the safety and activity of the 30-minute infusion at 2 dose levels (either 20/45 or the 20/56 mg/m<sup>2</sup>). A final report of the PK analysis will be submitted to the agency when the PX-171-007 trial is completed.
- The 2011-003 Study POP PK analysis will evaluate the effect of creatinine clearance on the carfilzomib clearance in 120 of the planned 888 patients. This study currently includes patients with creatinine clearance of  $\geq 15$  mL/min. The POP PK analysis will stratify patients according to renal function as part of the analysis.

Onyx would like to request an opportunity to further discuss the applicability of this Post Marketing Request to the current NDA under review.

**FDA Response (6/26/12):**

Our conclusions are that carfilzomib has renal and hepatic safety issues. The drug caused Grade 3/4 ALT increase in 6.4% of patients that were enrolled in the pivotal phase 2 trial, which is a relatively strong signal for liver toxicity. Also, there were signals of acute creatinine increase in clinical trials.

Additional factors that influenced our proposal for PMR studies:

- 2 patients had hepatic failure during clinical trial
- Patients with baseline liver impairment maybe at increased risk of drug-induced liver toxicity
- Rat excretion study indicated > 30% of the administered drug undergoes biliary elimination.

The hepatic impairment PMR would be acceptable provided the timeline is modified in line with the ENDEAVOR timelines.

**For the renal impairment PMR, you need to provide PK in chronic dialysis pts on the 30 min infusion dose.**

**ONYX RESPONSE (6/28/12):** In addition to the POP PK analyses of the effects of creatinine clearance on the PK parameters of carfilzomib, (*PX-171-009 and 2011-003*), Onyx agrees to conduct a stand-alone study in multiple myeloma patients on chronic dialysis. The trial will enroll patients to receive repeat doses of carfilzomib administered as a 30 minute infusion at 20/56 mg/m<sup>2</sup>. The trial will be conducted in accordance with applicable guidance documents. A draft protocol will be submitted to the Agency for review. Dates have been provided.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KAREN E BENGTSON  
07/05/2012

**Bengtson, Karen**

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**From:** Bengtson, Karen  
**Sent:** Tuesday, June 26, 2012 4:08 PM  
**To:** 'Ruben Sanchez'; Alison Cole  
**Subject:** RE: NDA 202714 Carfilzomib - Post-Marketing Requirements  
**Importance:** High  
**Attachments:** NDA 202714 Carfilzomib) PMRs\_Onyx Comments\_FDA Responses(26Jun2012).doc

Dear Alison and Ruben,

See the FDA responses to your preliminary comments received on June 22, 2012 regarding the proposed PMRs. Please let me know if your team will be available for a teleconference this Thursday, June 28, 2012 from 4:00 - 4:30 PM (ET) to discuss further.

Kind regards,  
Karen

**KAREN BENGTSON**

Regulatory Project Manager  
DHP/OHOP/CDER/FDA  
WO22, Room 2189  
Phone: 301-796-3338  
Fax: 301-796-9845  
E-mail: karen.bengtson@fda.hhs.gov

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**From:** Ruben Sanchez [mailto:rsanchez@onyx.com]  
**Sent:** Friday, June 22, 2012 6:56 PM  
**To:** Bengtson, Karen  
**Cc:** Alison Cole  
**Subject:** RE: NDA 202714 Carfilzomib - Post-Marketing Requirements

Hi Karen,

We have reviewed the draft post marketing requirements and are including here our preliminary responses/comments. We have also included proposed scheduled milestones. For those requirements that we feel warrant further clarification/discussion we have noted that in our response.

If you have any questions do not hesitate to contact Alison or myself.

Regards,  
Ruben

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**From:** Bengtson, Karen [mailto:Karen.Bengtson@fda.hhs.gov]  
**Sent:** Friday, June 15, 2012 5:34 AM  
**To:** Alison Cole  
**Cc:** Ruben Sanchez

**Subject:** RE: NDA 202714 Carfilzomib - Post-Marketing Requirements

Hi Alison,

I will request clarification from the team and get back to you.

Thank you,  
Karen

**KAREN BENGTON**

Regulatory Project Manager

DHP/OHOP/CDER/FDA

WO22, Room 2189

Phone: 301-796-3338

Fax: 301-796-9845

E-mail: [karen.bengtson@fda.hhs.gov](mailto:karen.bengtson@fda.hhs.gov)

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**From:** Alison Cole [<mailto:acole@onyx.com>]

**Sent:** Thursday, June 14, 2012 5:15 PM

**To:** Bengtson, Karen

**Cc:** Ruben Sanchez

**Subject:** RE: NDA 202714 Carfilzomib - Post-Marketing Requirements

Karen,

The study number for ASPIRE is PX-171-009.

Kind Regards,

Alison

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**From:** Alison Cole

**Sent:** Thursday, June 14, 2012 2:11 PM

**To:** 'Bengtson, Karen'

**Cc:** Ruben Sanchez

**Subject:** RE: NDA 202714 Carfilzomib - Post-Marketing Requirements

Dear Karen,

Onyx is preparing to put together comments to send to FDA by June 22<sup>nd</sup> per your e- mail below. We would like to ask the following clarification question:

PMR 1 states the following:

- **“PMR 1: Requirement under Subpart H to Verify Clinical Benefit**

To verify and describe the clinical benefit of carfilzomib, you agree to conduct one or more randomized controlled trials.

You agree to conduct a randomized controlled trial per Protocol 2011-003, as finalized, to

compare carfilzomib-dexamethasone with bortezomib-dexamethasone in a population of patients with myeloma, whose disease has relapsed after previous response to at least one but not more than three prior therapies, to assess efficacy and safety.....”

Question from Onyx: The Phase 3 ASPIRE trial which is being conducted under a SPA agreement with FDA was designed to confirm the clinical benefit of carfilzomib. If a favorable action occurs on July 27<sup>th</sup>, would the ASPIRE study fulfill the requirement for PMR 1?

Kind Regards,  
Alison

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**From:** Bengtson, Karen [<mailto:Karen.Bengtson@fda.hhs.gov>]  
**Sent:** Wednesday, June 13, 2012 1:01 PM  
**To:** Alison Cole  
**Subject:** NDA 202714 Carfilzomib - Post-Marketing Requirements  
**Importance:** High

Dear Alison,

As we continue our review of your NDA, our policy is to consider post-marketing studies and labeling so that they can be completed in advance of any action date. Based on the data available to date, we have determined that the attached clinical trials are necessary as post-marketing requirements (PMRs) should a favorable action occur. These brief summaries are intended to describe the main trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. We are available to discuss by teleconference, if needed.

Upon mutual agreement, we will ask you to submit an official copy of the PMR trials to the NDA with a statement that you agree to perform the trials as described and within the timelines that you specify for the trials. For initial planning purposes, you may propose tentative milestone times based on a time interval that would be feasible following an approval action date. Final PMR designation numbers will be assigned later.

Note that single-arm trials typically do not provide the strength of evidence to judge the safety of new drugs as do randomized controlled trials that isolate the effect of the investigational drug. The first four trials listed here are intended to assess treatment emergent toxicities. While accompanying PK information can be very useful in understanding the reasons for certain outcomes, and we encourage their incorporation, these are not primarily PK studies.

We request that you provide comments by Friday, June 22, 2012.

Please acknowledge receipt of this e-mail correspondence.

Kind regards,  
Karen

**KAREN BENGTSON**  
Regulatory Project Manager

Division of Hematology Products  
OHOP/CDER/FDA  
WO22, Room 2189  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
Phone: 301-796-3338  
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## **Summary of Post-Marketing Requirements (PMR) for Carfilzomib with Timelines**

### **PMRs under Accelerated Approval (Subpart H)**

#### **PMR 1: Requirement under Subpart H to Verify Clinical Benefit**

To verify and describe the clinical benefit of carfilzomib, you agree to conduct one or more randomized controlled trials.

You agree to conduct a randomized controlled trial per Protocol 2011-003, as finalized, to compare carfilzomib-dexamethasone with bortezomib-dexamethasone in a population of patients with myeloma, whose disease has relapsed after previous response to at least one but not more than three prior therapies, to assess efficacy and safety. Patients are required to show evidence of progression after prior therapy. Estimated sample size is 900. The randomization will balance known important prognostic factors. The goal of the trial is to demonstrate clinical and statistical superiority on the primary endpoint of progression-free survival (PFS) for the carfilzomib-containing arm, as determined by an independent review committee blinded to the treatment given.

In your response, please propose the following PMR Schedule milestones:

##### **PX-171-009 (ASPIRE) Phase 3 Study**

- a. Final Protocol Submission (01/2010)
- b. Trial Completion (current estimate based on event accrual projections: 12/2013)
- c. Final Report Submission (current estimate: 06/2014)

***ONYX RESPONSE (6/22/12): Onyx intends to fulfill the requirement under Subpart H to provided confirmation of clinical benefit through completion of the ASPIRE Trial (PX-171-009). This study protocol is being conducted under a Special Protocol Assessment and the PMR schedule milestones are noted above.***

**FDA Response (6/26/12): Accepted.**

**Note to applicant:** The dates have to be in final form (in month/year format) as part of the documentation of an approval action. For all PMRs, provide the dates you consider to be feasible in your reply. Once the dates are set by you, current rules do not allow changes.

### **PMRs under FDAAA**

#### **PMR 2: Cardiac Safety Trial**

Cardiac dysfunction is common in heavily pretreated multiple myeloma patients. Cardiac dysfunction has been observed with carfilzomib, and the safety of carfilzomib in the relapsed myeloma population is not well characterized.

Therefore, conduct a randomized clinical trial in patients receiving carfilzomib to identify and characterize the cardiac toxicities associated with carfilzomib. We suggest that you



consider doing this trial as a sub-study within your proposed Protocol 2011-003, or you may propose a separate trial with this safety objective. The primary objective is to compare changes in cardiac function between the group receiving carfilzomib and a control group not receiving carfilzomib in a parallel group trial.

If you choose to add this sub-study to your proposed protocol, the trial protocol must require a resting ECG and a baseline transthoracic ECHO to assess LVEF on all patients. If transthoracic ECHO is not available at some sites, MUGA will be acceptable for baseline screening LVEF evaluation. A subset of patients from both trial treatment arms should be assessed for LVEF and right ventricular (RV) function with transthoracic ECHO (or MUGA for those sites using MUGA at baseline) periodically throughout study treatment and at the time of the End-of-Treatment visit, using similar test procedures and equipment to allow serial intra-patient comparisons. The subset of patients must include a minimum of 100 patients and a maximum of 300 patients total (50 to 150 patients per treatment arm). Specific details regarding the interpretation of LVEF changes in the subset of patients must be pre-specified and outlined in the SAP for this sub-study. Readers of the ECHOs/MUGAs must be blinded to the treatment given.

In addition, any patient who has a cardiac adverse event (AE) that is considered a clinically significant AE must have an ECHO performed to assess left ventricular (LV) and right ventricular function as part of the evaluation of that AE; this AE evaluation applies to all patients enrolled in the trial.

Submit a complete protocol for review and concurrence before commencing the trial.

In your response, please propose the following PMR Schedule milestones:

2011-003 (ENDEAVOR) Phase 3 Study

- a. Final Protocol Submission (03/2012)
- b. Trial Completion (current estimate: 2<sup>nd</sup> Half/2015)
- c. Final Report Submission (current estimate: 2<sup>nd</sup> Half/2016)

Notes to Applicant:

1. For initial planning, you may indicate the number of months/years that you would consider to be feasible and occurring following an approval date.
2. The term “final protocol submission” means the protocol that has been agreed to by both the FDA and you and is in the final form for initiating the trial.

***ONYX RESPONSE (6/22/12): A cardiac sub-study is currently incorporated into Protocol 2011-003 (ENDEAVOR) as described above, and is designed to evaluate both left and right ventricular function in a subset of patients from both treatment arms in a serial fashion by central review. In addition, Protocol 2011-003 does specify i) baseline ECHO to be obtained on all patients, and ii) follow-up ECHO to be obtained on any patient who experiences a clinically significant cardiac adverse event.***

**FDA Response (6/26/12): Accepted, with final dates required.**

### PMR 3: Pulmonary Safety Trial

Pulmonary toxicities have been observed with carfilzomib, but they are not well characterized.

Therefore, conduct a randomized clinical trial in patients receiving carfilzomib to identify and characterize the pulmonary toxicities associated with carfilzomib. The primary objective is to compare pulmonary toxicities between the group receiving carfilzomib and a control group not receiving carfilzomib in a parallel group trial. This could be done within the proposed Protocol 2011-003 as a sub-study or as a separate trial as you prefer. If performed as a sub-study of protocol 2011-003, obtain this baseline exam on all patients enrolled in that trial, during screening, and to serve as the baseline ECHO for later comparisons on all patients. This study must include a baseline transthoracic ECHO to estimate the pulmonary artery pressures and to assess right ventricular size, thickness, and function. Subsequently, a subset of patients from both treatment arms should be assessed periodically for pulmonary artery pressures and right ventricular function with repeat transthoracic ECHO throughout study treatment and at the time of the End-of-Treatment visit, using similar test procedures and equipment to allow serial intra-patient comparisons. Emergent pulmonary toxicities must be further characterized in all patients receiving carfilzomib, to include at least the following: time course of onset and resolution, oximetry and/or blood gases, and consultation with a pulmonary specialist, when available, to provide further documentation of the nature of the emergent condition. Document the response to oxygen supplementation and other treatment measures.

A minimum of 100 patients and a maximum of 300 patients total are necessary (50 to 150 patients per treatment arm). Pre-specify how comparisons will be performed for changes between the two groups for outcomes related to pulmonary hypertension, right ventricular function, and clinical pulmonary safety events. Additionally, any patient who has a cardiac or pulmonary AE that is considered a clinically significant AE, must have a follow-up ECHO at the time of the event to assess LV, RV, and pulmonary artery function. This AE evaluation is for all patients enrolled in the study.

In your response, please propose the following PMR Schedule milestones:

#### 2011-003 (ENDEAVOR) Phase 3 Study

- a. Final Protocol Submission (03/2012)
- b. Trial Completion (2<sup>nd</sup> Half/2015)
- c. Final Report Submission (2<sup>nd</sup> Half/2016)

***ONYX RESPONSE (6/22/12): As noted in response to PMR 2, Onyx plans to obtain baseline ECHOs (or MUGA's when ECHO is not available) in all patients enrolled in Protocol 2011-003, and also to perform a sub-study on a subset of patients from each arm to allow serial intra-patient comparisons.***

***Onyx will develop an additional case report form in order to capture information regarding pulmonary studies performed and their results and will provide guidance to investigators in Protocol 2011-003 regarding recommended evaluations that may be performed in response to a clinically significant pulmonary adverse event. However,***

*Onyx is concerned about mandating additional evaluations in the setting of a Phase 3 trial because of potential negative impact on accrual.*

**FDA Response (6/26/12):** Accepted pending the following notes:

- a. The dates have to be in final form as part of the documentation.
- b. If dyspnea leads to the provision of supplemental oxygen, it is standard care as part of providing oxygen to measure systemic oxygen by any of several means, including oximetry. We consider these results important in assessing safety and reasonable to obtain per protocol.

#### **PMR 4: Study of Carfilzomib Administered as a 30-Minute Infusion**

The proposed dose of carfilzomib submitted as part of NDA 202714 is 20/27 mg/m<sup>2</sup> administered intravenously as a bolus over 2 to 10 min. Conduct a safety study using the 30 minutes intravenous infusion of carfilzomib at the dose of 20/56 mg/m<sup>2</sup> in patients with multiple myeloma.

Conduct your safety evaluation using either of the following two options or propose an alternative option for our review and concurrence:

- Conduct the study as part of the planned Phase 3 trial (Protocol number 2011-003)

OR

- Conduct a stand-alone safety study in patients receiving carfilzomib. Conduct the study for sufficient duration in order to detect and assess safety signals. If you choose to do a stand safety trial, submit a complete study protocol for review and concurrence.

In your response, please propose the following PMR Schedule milestones:

##### 2011-003 (ENDEAVOR) Phase 3 Study

- a. Final Protocol Submission (03/2012)
- b. Study Completion (2<sup>nd</sup> Half/2015)
- c. Final Report Submission (2<sup>nd</sup> Half/2016)

**ONYX RESPONSE (6/22/12):** *The safety assessment of the 30 minute infusion rate is one of the objectives of Protocol 2011-003. The safety will be submitted as part of the clinical study report for the trial. In addition, Onyx has completed the enrollment of 49 patients with multiple myeloma into the Phase 2 PX-171-007 study. This study is designed to evaluate the safety and activity of the 30-minute infusion at 2 dose levels (either 20/45 or the 20/56 mg/m<sup>2</sup>).*

**FDA Response (6/26/12):** Accepted. Please indicate that you agree to submit the results of both trials, as they separately become available, for this safety study.

**PK Trials:****PMR 5: Hepatic Impairment**

Conduct a clinical trial in patients with hepatic impairment to assess safety and PK characteristics of carfilzomib administered as a 30 minute infusion. The number of patients enrolled in the study should be sufficient to detect PK differences that would warrant dosage adjustment recommendations in the labeling. The duration of the study should be sufficient (several cycles) to reasonably characterize potential safety issues. The PK sampling scheme should be optimal to accurately estimate relevant PK parameters for the parent drug. A data analysis plan must be included in the protocol. Submit your protocol for Agency review and concurrence prior to initiation.

In your response, please propose the following PMR Schedule milestones:

Draft timeline for proposed phase 1 study post completion of PX-171-009

- a. Final Protocol Submission (1<sup>st</sup> Half/2015)
- b. Study Completion (2<sup>nd</sup> Half/2016)
- c. Final Report Submission (2<sup>nd</sup> Half/2016)

**ONYX RESPONSE (6/22/12):** *Onyx would like to further understand the Agency's concerns regarding administration of carfilzomib to patients with hepatic impairment to ensure the Onyx proposal meets the Agency's objectives. Carfilzomib is rapidly cleared from the plasma compartment with mean clearance values (150–263 L/hr at 20 and 27 mg/m<sup>2</sup>) that are greater than liver blood flow, suggesting that carfilzomib is cleared primarily extrahepatically. In animal studies, less than 1% of carfilzomib was excreted intact in bile. Carfilzomib is rapidly and systemically metabolized. The predominant metabolites in human plasma and urine, and those generated in vitro by human hepatocytes, are peptide fragments of the parent drug (M14 and M15) and carfilzomib diol (M16), suggesting that peptidase cleavage and epoxide hydrolysis are principal pathways of metabolism. These metabolites are formed immediately after administration and are inactive. In view of these data, no formal study was conducted to assess carfilzomib PK in patients with hepatic impairment.*

*Onyx would like to request an opportunity to further discuss the applicability of this Post Marketing Request to the current NDA under review.*

**FDA Response (6/26/12):** See response under PMR 6

**PMR 6: Renal Impairment**

Since PK assessment in the renal impairment study was conducted following carfilzomib doses of 15/20 mg/m<sup>2</sup> given intravenously over 2 – 10 minutes and since this dosing regimen may not necessarily produce clinical responses at the level that would be seen with higher doses, evaluate the PK, safety, and efficacy of carfilzomib in patients with varying degrees of renal impairment following the administration of carfilzomib when given as a 30 minute intravenous infusion at a sufficient dose level that will likely produce comparable exposure and clinical response to those patients without renal impairment that receive carfilzomib doses of 20/56 mg/m<sup>2</sup> using the 30 minute infusion

as planned in your upcoming Phase 3 trial Protocol number 2011-003. Collect PK samples following carfilzomib doses of 56 mg/m<sup>2</sup> or highest clinical dose in the protocol. Conduct your renal impairment evaluation using either of the following two options or propose an alternative option for our review and concurrence:

- Amend the planned Phase 3 trial (Protocol number 2011-003) to include patients with varying degrees of renal impairment and those on chronic dialysis.

OR

- Conduct a stand-alone renal impairment study in patients with varying degrees of renal impairment including patients with mild, moderate, severe renal function and those on chronic dialysis. Conduct the study for sufficient duration in order to detect and assess safety and efficacy signals. If you choose to do a stand-alone renal impairment trial, submit a complete study protocol for review and concurrence by the Agency.

In your response, please propose the following PMR Schedule milestones:

2011-003 (ENDEAVOR) Phase 3 Study

- a. Final Protocol Submission (03/2012)
- b. Study Completion (2<sup>nd</sup> Half/2015)
- c. Final Report Submission (2<sup>nd</sup> Half/2016)

***ONYX RESPONSE (6/22/12): In Study PX-171-005, the sponsor established that the pharmacokinetics (PK) of carfilzomib delivered over 2 – 10 minutes at 15 and 20 mg/m<sup>2</sup> to multiple myeloma patients was not affected by renal status including patients on chronic dialysis. Carfilzomib was well tolerated and active in patients with renal impairment in this study. Therefore, no dose adjustment for patients with renal insufficiency including patients on dialysis is recommended and proposed for the label. Onyx will continue to evaluate the PK, safety and efficacy of carfilzomib in patients with mild renal insufficiency:***

- ***PX-171-009 POP PK analysis will evaluate the effect of creatinine clearance on the plasma clearance of carfilzomib.***
- ***Onyx has completed the enrollment of 49 patients with multiple myeloma into the Phase 2 PX-171-007 study. This study is designed to evaluate the safety and activity of the 30-minute infusion at 2 dose levels (either 20/45 or the 20/56 mg/m<sup>2</sup>). A final report of the PK analysis will be submitted to the agency when the PX-171-007 trial is completed.***
- ***The 2011-003 Study POP PK analysis will evaluate the effect of creatinine clearance on the carfilzomib clearance in 120 of the planned 888 patients. This study currently includes patients with creatinine clearance of ≥ 15 mL/min. The POP PK analysis will stratify patients according to renal function as part of the analysis.***

***Onyx would like to request an opportunity to further discuss the applicability of this Post Marketing Request to the current NDA under review.***

**FDA Response (6/26/12):**

**Our conclusions are that carfilzomib has renal and hepatic safety issues. The drug caused Grade 3/4 ALT increase in 6.4% of patients that were enrolled in the pivotal phase 2 trial, which is a relatively strong signal for liver toxicity. Also, there were signals of acute creatinine increase in clinical trials.**

**Additional factors that influenced our proposal for PMR studies:**

- **2 patients had hepatic failure during clinical trial**
- **Patients with baseline liver impairment maybe at increased risk of drug-induced liver toxicity**
- **Rat excretion study indicated > 30% of the administered drug undergoes biliary elimination.**

**The hepatic impairment PMR would be acceptable provided the timeline is modified in line with the ENDEAVOR timelines.**

**For the renal impairment PMR, you need to provide PK in chronic dialysis pts on the 30 min infusion dose.**

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/s/  
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KAREN E BENGTSON  
07/05/2012

**Bengtson, Karen**

---

**From:** Bengtson, Karen  
**Sent:** Tuesday, June 26, 2012 1:49 PM  
**To:** 'Alison Cole'  
**Subject:** NDA 202714 - Promotional Materials

Dear Alison,

Please refer to your New Drug Application (NDA) dated September 26, 2011 (received September 27, 2011) under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carfilzomib (PR-171) for Injection.

We are reviewing this application under the provisions of 21 CFR 314 Subpart H – *Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses*. Unless we otherwise inform you, as required by 21 CFR 314.550, you must submit during the preapproval review period copies of all promotional materials, including promotional labeling and advertisements, intended for dissemination or publication within 120 days following marketing approval (i.e., your launch campaign). During the preapproval review period, please submit, in triplicate, a detailed cover letter (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

FDA proposed revisions to the package insert (PI) were sent to you on June 22, 2012. Submit launch materials when you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

Best regards,  
Karen

**KAREN BENGTSON**  
Regulatory Project Manager  
Division of Hematology Products  
OHOP/CDER/FDA  
WO22, Room 2189  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
Phone: 301-796-3338  
Fax: 301-796-9845  
E-mail: karen.bengtson@fda.hhs.gov

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/s/  
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KAREN E BENGTSON  
06/26/2012

## Bengtson, Karen

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**From:** Bengtson, Karen  
**Sent:** Friday, June 22, 2012 4:40 PM  
**To:** 'Alison Cole'  
**Cc:** 'Ruben Sanchez'  
**Subject:** NDA 202714 - Carfilzomib - Draft Package Insert

**Importance:** High

**Attachments:** NDA 202714-cfz-draft-PI-FDA Revisions (22Jun2012).doc

Dear Alison,

Attached is the Carfilzomib package insert (PI) for NDA 202714 based on FDA review. In order to facilitate negotiations, we request that you respond by close of business, Wednesday, June 27, 2012.

Where Onyx agrees with the labeling, please accept the tracked changes. Where Onyx does not agree with the labeling revisions, please provide your comments and proposed language (shown in tracked-changes). Also, please review the document for formatting, spacing and margins.

Please confirm receipt of this e-mail correspondence. If you have any questions, please feel free to contact me.

Kind regards,  
Karen



NDA  
14-cfz-draft-PI-FDA

**KAREN BENGTSON**  
Regulatory Project Manager  
Division of Hematology Products  
OHOP/CDER/FDA  
WO22, Room 2189  
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Silver Spring, MD 20993  
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47 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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KAREN E BENGTSON  
06/22/2012

## Bengtson, Karen

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**From:** Bengtson, Karen  
**Sent:** Wednesday, June 13, 2012 4:01 PM  
**To:** 'Alison Cole'  
**Subject:** NDA 202714 Carfilzomib - Post-Marketing Requirements

**Importance:** High

**Attachments:** NDA 202714 Carfilzomib) PMRs\_(13June2012).doc

Dear Alison,

As we continue our review of your NDA, our policy is to consider post-marketing studies and labeling so that they can be completed in advance of any action date. Based on the data available to date, we have determined that the attached clinical trials are necessary as post-marketing requirements (PMRs) should a favorable action occur. These brief summaries are intended to describe the main trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. We are available to discuss by teleconference, if needed.

Upon mutual agreement, we will ask you to submit an official copy of the PMR trials to the NDA with a statement that you agree to perform the trials as described and within the timelines that you specify for the trials. For initial planning purposes, you may propose tentative milestone times based on a time interval that would be feasible following an approval action date. Final PMR designation numbers will be assigned later.

Note that single-arm trials typically do not provide the strength of evidence to judge the safety of new drugs as do randomized controlled trials that isolate the effect of the investigational drug. The first four trials listed here are intended to assess treatment emergent toxicities. While accompanying PK information can be very useful in understanding the reasons for certain outcomes, and we encourage their incorporation, these are not primarily PK studies.

We request that you provide comments by Friday, June 22, 2012.

Please acknowledge receipt of this e-mail correspondence.



NDA 202714  
arfilzomib) PMRs\_(.

Kind regards,  
Karen

**KAREN BENGTON**  
Regulatory Project Manager  
Division of Hematology Products  
OHOP/CDER/FDA  
WO22, Room 2189  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
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/s/  
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KAREN E BENGTSON  
06/13/2012

## Bengtson, Karen

---

**From:** Bengtson, Karen  
**Sent:** Friday, June 08, 2012 4:46 PM  
**To:** 'Alison Cole'  
**Cc:** Ruben Sanchez; Sheldon Mullins  
**Subject:** NDA 202714 Carfilzomib - Clinical Information Request

**Importance:** High

Dear Alison,

Please refer to your New Drug Application (NDA) dated September 26, 2011 (received September 27, 2011) under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carfilzomib (PR-171) for Injection.

We are reviewing your submission and have the following information request. We request a written response via email by 5:00 PM (EST) on June 12, 2012 in order to continue our evaluation of your NDA. You will also need to follow up with a formal response to the NDA.

### CLINICAL

- Provide an explanation as to why there are 371 patients among the 526 patients with multiple myeloma enrolled in Phase 2 studies that have an AST elevation (Grades 1 to 4 under the column LBTOXGR) in ADLBPH2 data files (combined ADLBPH21, ADLBPH22, and ADLBPH23), but the adverse event incidence of Aspartate aminotransferase increased in Table 5 of the proposed label submitted with the NDA is 12.5% of patients from the 526 patients with multiple myeloma enrolled in Phase 2 studies.

Please acknowledge receipt of this e-mail correspondence.

Kind regards,  
Karen

**KAREN BENGTSON**  
Regulatory Project Manager  
Division of Hematology Products  
OHOP/CDER/FDA  
WO22, Room 2189  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
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/s/  
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KAREN E BENGTSON  
06/08/2012





DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 202714

Onyx Pharmaceuticals, Inc.  
Attention: Alison Cole  
Senior Director, Regulatory Affairs  
249 East Grand Avenue  
South San Francisco, CA 94080

Dear Ms. Cole:

Please refer to your September 26, 2011 (received September 27, 2011) New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carfilzomib (PR-171) for Injection.

We also refer to our December 8, 2011, letter in which we notified you of our target date of June 8, 2012 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals And Procedures – Fiscal Years 2008 Through 2012."

Although we are not prepared for the discussion of the draft labeling and draft postmarketing requirements/commitments today, these draft documents will be forthcoming as promptly as possible.

This notification does not reflect a final decision on the information under review.

If you have any questions, contact me at (301) 796-3338 or Karen.Bengtson@fda.hhs.gov.

Sincerely,

*{See appended electronic signature page}*

Karen Bengtson  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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KAREN E BENGTSON  
06/08/2012

## Bengtson, Karen

---

**From:** Bengtson, Karen  
**Sent:** Friday, May 18, 2012 8:44 AM  
**To:** 'Alison Cole'  
**Cc:** Sheldon Mullins; Ruben Sanchez  
**Subject:** NDA 202714 (Carfilzomib) - Information Request - Container Label

**Importance:** High

Dear Ms. Cole:

Please refer to your New Drug Application (NDA) submitted September 26, 2011 (received September 27, 2011) under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carfilzomib (PR-171) for Injection.

We also refer to your amendment dated May 14, 2012 containing revised carton and container labeling.

We are reviewing your amendment and have the following comments regarding the container label. We request a response by May 25, 2012 in order to continue our evaluation of your supplemental application.

### CONTAINER LABEL:

- 1) Remove what appears to be a line under the statement "For Intravenous Administration Only."
- 2) Increase the white space between the "Discard unused portion" and "For Intravenous Administration Only" statements (i.e., similar to the appearance on the carton labeling).

Please acknowledge receipt of this e-mail correspondence.

Kind regards,  
Karen

**KAREN BENGTSON**  
Regulatory Project Manager  
Division of Hematology Products  
OHOP/CDER/FDA  
WO22, Room 2189  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
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/s/  
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KAREN E BENGTSON  
05/18/2012

**Bengtson, Karen**

---

**From:** Bengtson, Karen  
**Sent:** Wednesday, May 16, 2012 11:31 AM  
**To:** 'Alison Cole'  
**Cc:** Ruben Sanchez; Sheldon Mullins  
**Subject:** NDA 202714 (Carfilzomib) - Clinical Information Request

**Importance:** High

Dear Alison,

Please refer to your New Drug Application (NDA) dated September 26, 2011 (received September 27, 2011) under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carfilzomib (PR-171) for Injection.

We also refer to your amendment dated November 18, 2011 containing your response to our October 18, 2011 request for information.

We are reviewing your submission and have the following information requests. We request a written response to points 1 and 2 via email by 5:00 PM on May 18, 2012 and point 3 by May 21, 2012 in order to continue our evaluation of your NDA. You will also need to follow up with a formal response to the NDA.

**CLINICAL**

1. Provide a definition for the term *Unresponsive or Intolerant* used in your November 18, 2011 amendment.

2. Provide the following information for all responders in Study PX-171-003A1 using the following definition:

The date of the evaluation that first documented response (sCR, CR, VGPR, or PR) to the date of the evaluation that was the last evaluation to document response prior to the date on which progression was documented. Please note that this definition of the duration of response differs from that you used to calculate the duration of response.

Use this information to calculate for each responding patient the duration of response, and provide the primary data and the calculated interval for each responding patient in a SAS transport file.

3. Provide an analysis of dyspnea observed in the Phase 2 multiple myeloma safety population.
  - How many of the adverse events described as dyspnea were adverse events associated with infusion reactions vs. organ system failure (cardiac, pulmonary vasculature, or parenchyma pulmonary tissue injury)?
  - How many were rapidly reversible vs. those which required a longer time to resolve?
  - How many did not resolve?

Please acknowledge receipt of this e-mail correspondence.

Kind regards,

Karen

**KAREN BENGTSON**

Regulatory Project Manager

Division of Hematology Products

OHOP/CDER/FDA

WO22, Room 2189

10903 New Hampshire Avenue

Silver Spring, MD 20993

Phone: 301-796-3338

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/s/  
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KAREN E BENGTSON  
05/17/2012

## Bengtson, Karen

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**From:** Bengtson, Karen  
**Sent:** Friday, May 11, 2012 9:19 AM  
**To:** 'Alison Cole'  
**Cc:** Ruben Sanchez; 'Sheldon Mullins'  
**Subject:** NDA 202714 - Information Request - Carton and Container Labeling

**Importance:** High

**Attachments:** NDA 202714 \_Carfilzomib\_ Container Label Comments\_\_10May2012.pdf; NDA 202714 \_Carfilzomib\_ Carton Labeling Comments\_\_10May2012.pdf

Dear Ms. Cole:

Please refer to your New Drug Application (NDA) submitted September 26, 2011 (received September 27, 2011) under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carfilzomib (PR-171) for Injection.

We are reviewing the labeling of your submission and have comments regarding the carton and container labeling (see attached). We request a written response by May 14, 2012 in order to continue our evaluation of your supplemental application.



NDA 202714  
Carfilzomib\_ Conta.



NDA 202714

Carfilzomib\_ Carto.

Please confirm receipt of this e-mail correspondence.

Kind regards,  
Karen

**KAREN BENGTSON**  
Regulatory Project Manager  
Division of Hematology Products  
OHOP/CDER/FDA  
WO22, Room 2189  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
Phone: 301-796-3338  
Fax: 301-796-9845  
E-mail: karen.bengtson@fda.hhs.gov

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1. Ensure the prominence of the established name (including the dosage form “for Injection”) is at least  $\frac{1}{2}$  the size of the proprietary name taking into account typography, layout, contrast, and other printing features to ensure it has prominence commensurate with the proprietary name as per 21 CFR 201.10(g)(2).
2. Revise the presentation of the strength statement to read “60 mg per vial” or “60 mg/vial”.
3. Remove the words (b) (4) following the strength designation as it is redundant and crowds the label.
4. Remove the word (b) (4) “Single-Use Vial” as it is unnecessary information and crowds the label.
5. Revise the statement (b) (4) to read “Single-use vial. Discard unused portion. (b) (4) The statement “Discard unused portion.” further serves as an important reminder that unused portion should be discarded.
6. Revise the composition statement to “Each vial contains 60 mg carfilzomib, 3,000 mg of sulfobutylether beta-cyclodextrin, and 57.6 mg anhydrous citric acid. After reconstitution with 29 mL of Sterile Water for Injection, USP, the concentration of Kyprolis is 2 mg/mL.”

Recommended Dosage: See Prescribing Information

7. Relocate the statement “For Intravenous Administration Only.” from the side panel to the front panel and ensure equal prominence to the statement “Single-use vial. Discard unused portion.” However, the use of adequate white space separating these statements is necessary since close proximity of these statements may lead healthcare professionals to misinterpret the meaning as giving the entire vial via intravenous route of administration.
8. Replace the hyphen within the temperature designations with the word “to” for improved clarity and to be consistent with USP standards. We recommend not using the hyphen between the numbers since a hyphen can be misinterpreted as a minus sign when discussing temperatures. Therefore, revise the statement to read “Store refrigerated at 2°C to 8°C (36°F to 46°F)”.
9. Add the strength designation “60 mg per vial” to the top flap of the carton labeling under the established name.
10. Reduce the prominence of the company name “ONYX” and the red circular graphic on the side panel. As currently presented, the company name may be misinterpreted as the product name.

1. Ensure the prominence of the established name (including the dosage form “for Injection”) is at least  $\frac{1}{2}$  the size of the proprietary name taking into account typography, layout, contrast, and other printing features to ensure it has prominence commensurate with the proprietary name as per 21 CFR 201.10(g)(2).
2. Revise the presentation of the strength statement to read “60 mg per vial” or “60 mg/vial”.
3. Remove the words (b) (4) following the strength designation as it is redundant and crowds the label.
4. Remove the word (b) (4) “Single-Use Vial” as it is unnecessary information and crowds the label.
5. Revise the statement (b) (4) to read “Single-use vial. Discard unused portion.” (b) (4)  
 (b) (4) The statement “Discard unused portion.” further serves as an important reminder that unused portion should be discarded.
6. Reduce the font size, unbold, and relocate the statement “Rx only” to the bottom of the label to reduce crowding near the strength and other important information.
7. Revise the composition statement to “Each vial contains 60 mg carfilzomib, 3,000 mg of sulfobutylether beta-cyclodextrin, and 57.6 mg anhydrous citric acid. After reconstitution with 29 mL of Sterile Water for Injection, USP, the concentration of Kyprolis is 2 mg/mL.”  
 Recommended Dosage: See Prescribing Information
8. Relocate the statement “For Intravenous Administration Only.” from the side panel to the front panel and ensure equal prominence to the statement “Single-use vial. Discard unused portion.” However, the use of adequate white space separating these statements is necessary since close proximity of these statements may lead healthcare professionals to misinterpret the meaning as giving the entire vial via intravenous route of administration.

- 
9. Replace the hyphen within the temperature designations with the word “to” for improved clarity and to be consistent with USP standards. We recommend not using the hyphen between the numbers since a hyphen can be misinterpreted as a minus sign when discussing temperatures. Therefore, revise the statement to read “Store refrigerated at 2°C to 8°C (36°F to 46°F)”.
  10. Reduce the prominence of the manufacturer’s information to avoid competing with other important information.

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/s/  
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KAREN E BENGTSON  
05/11/2012

## Bengtson, Karen

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**From:** Bengtson, Karen  
**Sent:** Friday, April 27, 2012 3:27 PM  
**To:** Alison Cole  
**Cc:** 'Ruben Sanchez'; 'Sheldon Mullins'  
**Subject:** NDA 202714 (Carfilzomib) - CMC Information Request

**Importance:** High

Dear Ms. Cole:

Please refer to your New Drug Application (NDA) submitted September 26, 2011 (received September 27, 2011) under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carfilzomib (PR-171) for Injection.

We are reviewing your submission and have the following information requests. We request a written response by 5:00 PM (EST) on May 1, 2012 in order to continue our evaluation of your NDA.

Chemistry, Manufacturing and Controls:

1. Include a test and acceptance criterion for (b) (4) in your drug product specification.
2. Tighten the acceptance criteria for the related substances (b) (4) based on the stability tests results or provide additional justification.
3. Evaluate the drug product for compounds that may leach from (b) (4) components of the container closure system. Establish appropriate validated analytical procedures to identify, monitor, and quantify leached components in the drug product, and propose acceptance criteria for the levels of leached compounds in the formulation. Additionally, provide leachable assessment of (b) (4) from IV bags and administration sets recommended for the intravenous infusion of Carfilzomib for Injection. Establish appropriate validated analytical procedures to identify, monitor, and quantify leached components (b) (4) in the drug product, and propose acceptance criteria for the levels of leached compounds in the infusion solution.

Please acknowledge receipt of this e-mail correspondence.

Kind regards,

**KAREN BENGTSON**  
Regulatory Project Manager  
Division of Hematology Products  
OHOP/CDER/FDA  
WO22, Room 2189  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
Phone: 301-796-3338  
Fax: 301-796-9845  
E-mail: karen.bengtson@fda.hhs.gov

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/s/  
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KAREN E BENGTSON  
04/27/2012



## Bengtson, Karen

---

**From:** Bengtson, Karen  
**Sent:** Thursday, April 12, 2012 1:11 PM  
**To:** 'Alison Cole'  
**Cc:** Sheldon Mullins; Ruben Sanchez  
**Subject:** NDA 202714 Carfilzomib - Clinical Pharmacology Information Request

**Importance:** High

**Attachments:** Picture (Enhanced Metafile)

Dear Ms. Cole:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carfilzomib (PR-171) for Injection.

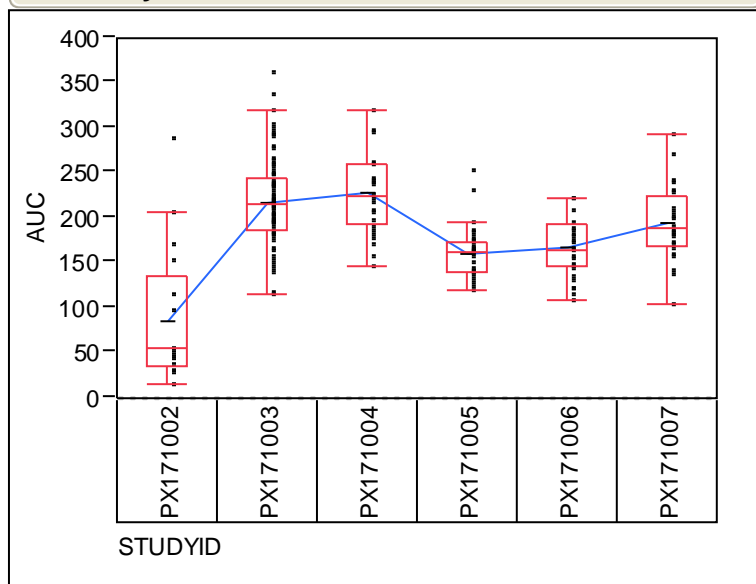
We also refer to your April 9, 2012 submission containing pharmacokinetic data for Study PX-171-002 in response to our March 29, 2012 information request.

We are reviewing your submission and have the following comments and information requests. We request a written response by April 16, 2012 in order to continue our evaluation of your NDA.

### **Clinical Pharmacology:**

It appears carfilzomib plasma concentration values collected in study PX-171-002 are much lower than plasma concentrations collected in other studies. For example, following 20 mg/m<sup>2</sup> dose of carfilzomib, observed Day 1 Cycle 1 (D1C1) AUC values for study PX-171-002 are much lower than the simulated AUC values for the other studies as depicted in the figure below. Please provide appropriate justification for the occurrence of approximately 2-fold lower AUC in study PX-171-002 compared to the other five studies. All AUC units are in hr·ng/mL.

**Variability Chart for AUC**



If you have any questions, feel free to contact me.

Sincerely,

**KAREN BENGTON**

Regulatory Project Manager

Division of Hematology Products

OHOP/CDER/FDA

WO22, Room 2189

10903 New Hampshire Avenue

Silver Spring, MD 20993

Phone: 301-796-3338

Fax: 301-796-9845

E-mail: karen.bengtson@fda.hhs.gov

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/s/  
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KAREN E BENGTSON  
04/12/2012



NDA 202714

**INFORMATION REQUEST**

Onyx Pharmaceuticals, Inc.  
Attention: Alison Cole  
Senior Director, Regulatory Affairs  
249 East Grand Avenue  
South San Francisco, CA 94080

Dear Ms. Cole:

Please refer to your New Drug Application (NDA) submitted September 26, 2011 (received September 27, 2011) under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carfilzomib (PR-171) for Injection.

We are reviewing your submission and have the following comments and information requests. We request a written response by April 27, 2012 in order to continue our evaluation of your NDA.

**Chemistry, Manufacturing and Controls:**

1. Identify the specific tests to be performed b [REDACTED] (b) (4)
2. Regarding the proposed manufacturing process and controls:

[REDACTED] (b) (4)

(b) (4)



3. Regarding the proposed specifications for starting materials:

(b) (4)



4. Regarding the proposed raw material specifications:

(b) (4)



5. Regarding the proposed in-process controls for intermediates:

(b) (4)

6. Regarding the structure elucidation studies:

(b) (4)

7. Regarding the proposed regulatory specification:

- a. Describe the specific rotation values for the known impurities in bulk drug substance with asymmetric centers.
- b. Explain why a test for purity (assay corrected for impurities and solvents) is not included.
- c. The proposed limits for (b) (4) are not supported by the submitted batch analysis and stability data. The submitted data shows test results well below the proposed limits.
- d. For each analytical method, provide the version number and the effective date.
- e. For method (b) (4), describe the preparation of the (b) (4) sensitivity solution used for system suitability testing.
- f. Revise method (b) (4) to report a specific test value (so that trend analysis may be performed).

8. Regarding the method validation studies:

- a. For method (b) (4), provide copies of representative chromatograms showing the effect from each variation in the ruggedness study addressed in Onyx Report TR-0441-171.
- b. For method (b) (4) submit validation data to support the linearity and accuracy over (b) (4) of the proposed limit, and the ruggedness of the method.

9. Either provide a copy of Federal Standard [REDACTED] (b) (4) or specify where this document is described.
10. Regarding the submitted stability information:
  - a. Revise the registration stability protocol to include specific rotation.
  - b. The photostability study on solid drug substance shows no degradation, however the forced degradation study for light stress of solid drug substance shows significant degradation [REDACTED] (b) (4). Explain how these contradictory study results support your conclusion that light protection is not needed during the manufacturing process.

If you have any questions, contact me at (301) 796-3338 or Karen.Bengtson@fda.hhs.gov.

Sincerely,

*{See appended electronic signature page}*

Karen Bengtson  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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KAREN E BENGTSON  
04/10/2012



**Bengtson, Karen**

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**From:** Bengtson, Karen  
**Sent:** Tuesday, April 03, 2012 11:26 AM  
**To:** 'Alison Cole'  
**Cc:** John Bedard; Ruben Sanchez  
**Subject:** RE: NDA 202714 (Carfilzomib) - Questions for Potential Telecon

Dear Ms. Cole,

Thank you for your email message of March 6, 2012 which contained a set of 3 questions to be discussed during a T-con proposed by Onyx “to obtain feedback from the FDA on the patient population for the carfilzomib NDA currently under review” in order “to discuss the FDA’s thoughts on the double refractory/intolerant population that we (Onyx) discussed at the January 9<sup>th</sup> walk-through meeting.”

FDA has provided responses to each of these 3 questions (see below). Since the FDA has answered in full the questions from Onyx, FDA believes that a T-con is unnecessary at this time. However, as the time of the upcoming ODAC draws near, the FDA would be willing to schedule a T-con with Onyx.

**Question #1 from Onyx:**

*Does FDA view the “double refractory/intolerant” population as appropriate for the basis of accelerated approval of carfilzomib?*

**FDA Response to Question #1:**

No. If Onyx is referring to its pivotal Phase 2 single-arm trial PX-171-003, FDA does not view the “double refractory/intolerant” population as appropriate for the basis of accelerated approval of carfilzomib.

In the November 4, 2011 T-con between FDA and Onyx, FDA provided Onyx with the following advice regarding the study population for a single-arm Phase 2 trial intended for the accelerated approval pathway:

- a. Available therapy is defined as all of the agents for which full approval has been granted for the indication in question.
- b. FDA must adhere to the regulations for accelerated approval which state that for a drug to be approved by the accelerated approval mechanisms, the proposed drug must provide meaningful therapeutic benefit over existing treatments to patients unresponsive to or intolerant of available therapy.

Available therapy is considered as therapy that is specified in the approved labeling of regulated products, with only rare exceptions. This is outlined in the Guidance for Industry on Available Therapy (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071>)

In response to Onyx’s question in the November 4, 2011 T-con as to whether FDA considers carmustine as available therapy because it is used for palliative care, FDA recommended that Onyx present their justification as to why patients are not candidates for carmustine or why exposure to carmustine is not appropriate for these patients. The submitted justification from Onyx is currently under review.

**During the January 9, 2012 Sponsor Orientation Meeting,** Dr. Richard Pazdur stated that the “double

refractory” myeloma population might be relevant to defining a population for a single-arm trial for accelerated approval if the applicant is able to demonstrate that the response to anthracyclines and alkylating agents, in a “double refractory” population is negligible. During this orientation meeting, Onyx stated that a publication by S. Kumar (Leukemia 26: 149, 2012) contains data that shows that this is indeed the case. At that time, FDA suggested that the applicant submit data showing that in a population that is relapsed/refractory to bortezomib and at least one of the IMiDs (lenalidomide or thalidomide), the response rate to anthracycline and alkylating agent based combination chemotherapy is negligible. While this approach could bolster the sponsor’s contention that the analysis of the submitted primary efficacy study (PX-171-003A1) should be restricted to patients entered on the trial who are “double refractory”, rather than to include the entire ITT population, FDA reminds the sponsor that in single-arm Phase II trials being used to support a marketing approval through the accelerated approval pathway, study subjects, with rare exceptions, are patients who have been exposed to and found to be resistant to all approved therapy.

FDA review of the Kumar paper (Leukemia 26: 149, 2012) cited by Onyx during the January 9, 2012 meeting revealed that the ORR (PR or greater) to combinations based on anthracyclines and alkylating agents was 24% in a double refractory population (which is higher, not lower than carfilzomib) in their primary efficacy study submitted in NDA 202714.

On January 10, 2012, FDA requested that the sponsor provide data showing that the ORR was negligible to anthracyclines and alkylating agent based chemotherapy in a population of myeloma patients who are “double refractory”.

**On February 15, 2012, Onyx submitted a formal response to the Information Request of January 10, 2012.** This response included as attachments the Kumar paper (Leukemia 26: 149, 2012) which showed a 24% ORR to anthracyclines and alkylating agents in the double refractory population, and 4 other publications:

1. Rivell et al Am J Hematology 86: 699, 2011 (letter), response to high dose cyclophosphamide with a response rate of 53% in a population of myeloma and plasma cell leukemia;
2. Mohty et al, Leukemia 26: 73, 2012 (a review) which quoted experience relating to double negative patients responding to bortezomib and lenalidomide;
3. Ruckser et al (ASH abstract): ASH abstracts 110: 4838, 2007 which is a case report of one patient who was double resistant and responded to a combination of lenalidomide, bortezomib, Doxil and dexamethasone, and
4. (b) (4)

This submission included a table (Table I, 5.3.5.3) summarizing the response rates in the double refractory population to combination chemotherapy based on anthracyclines and alkylating agents. This was attributed to Kumar et al, 2011, but no reference given (just the 2012 Leukemia reference). This table contained ORR ranging from 0% (for VAD) to 67% with several of them being in the 30-50% range.

In addition, this submission contains an exploratory analysis conducted by Onyx using data from the primary efficacy study (PX 171-003A1) of the “last prior therapy in double refractory/intolerant patients”. Two hundred and twenty eight out of the 266 patients enrolled in the study were identified who were double refractory (147 acquired this status before the last prior therapy before entry onto PX-171-003A1). Of these, 66 had received a regimen containing an alkylating agent or an anthracycline prior to carfilzomib. This data, summarized in Table 2 (5.23.5.3-see attached report) showed ORR

ranging from 0% for anthracycline as a single agent (1 patient), to 46% (anthracycline containing last regimen not in combination with bortezomib or lenalidomide or thalidomide), 32% (all anthracycline containing regimens in 31 patients), and 36% for alkylating agent based regimens as the last regimen not a part of transplant before entering onto PX-171-003A1.

The totality of the data suggests that the ORR to anthracycline and alkylating agent based chemotherapy in a double refractory population of myeloma patients is higher (not lower) than the ORR to carfilzomib recorded in the primary efficacy study (FDA result, ORR approximately 22%). FDA finds that the answer provided by Onyx in the February 15, 2012 submission to Dr. Pazdur's request posed to Onyx during the January 9, 2012 meeting: "Please submit the data showing that in a population relapsed/refractory to bortezomib and one of the two IMiDs is negligible to anthracycline and alkylating agent based combination chemotherapy", is that response rates in the double negative population to anthracycline and alkylating agent based combination chemotherapy are higher than the overall response rate seen in the ITT population in Study PX-171-003A1. This also applies to the subset of patients entered into PX-171-003 who had been exposed to and found to be resistant to all approved agents.

In addition to the ORR data, Onyx provided an analysis in the February 15, 2012 report suggesting that the duration of the responses to carfilzomib seen in PX-171-003A1 had a median duration of response of 7.4 months, and that the duration of responses to alkylating agent and anthracycline based chemotherapy ranged between 1-6 months.

FDA has the following comments in response to these findings:

- Summaries of response duration are usually for responders only, which is not a random subset of the entire population (unless the response rate is 100%). This makes it difficult, even in a randomized study, to statistically compare duration of response. FDA has informed sponsors in the past, who have used duration of response as a secondary endpoint with intention to do comparisons that since having a tumor response is a treatment related outcome, formal statistical comparisons of duration of response will not be interpretable.
- Estimates of Medians are not very precise and become less precise the smaller the collection of values.

**Question #2 from Onyx:**

*Does FDA require any additional analyses to support a potential approval?*

**FDA Response to Question #2:**

See response to Question #1.

**Question #3 from Onyx:**

*Does FDA have any specific guidance for Onyx in preparing for an ODAC Meeting?*

**FDA Response to Question #3**

See response to Question #1.

Kind regards,  
Karen

KAREN BENGTON  
Regulatory Project Manager  
DHP/OHOP/CDER/FDA

WO22, Room 2189  
Phone: 301-796-3338  
Fax: 301-796-9845  
E-mail: karen.bengtson@fda.hhs.gov

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**From:** Alison Cole [mailto:[acole@onyx.com](mailto:acole@onyx.com)]  
**Sent:** Tuesday, March 06, 2012 12:32 PM  
**To:** Bengtson, Karen  
**Cc:** John Bedard; Ruben Sanchez  
**Subject:** NDA 202714 (Carfilzomib) - Questions for Potential Telecon

Dear Karen,

Please find attached some questions for a potential telecon between Onyx and FDA.

Kind Regards,  
Alison

**Alison T. Cole**  
Senior Director | Regulatory Affairs  
Onyx Pharmaceuticals Inc | 249 E. Grand Ave., | South San Francisco | CA 94080  
direct: 650.266.1672  
cell: 510.289.8523  
[acole@onyx-pharm.com](mailto:acole@onyx-pharm.com)

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/s/  
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KAREN E BENGTSON  
04/03/2012

**Bengtson, Karen**

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**From:** Bengtson, Karen  
**Sent:** Thursday, March 29, 2012 3:07 PM  
**To:** 'Alison Cole'  
**Cc:** Ruben Sanchez; Sheldon Mullins; John Bedard  
**Subject:** RE: NDA 202714 (Carfilzomib) - Clinical Pharmacology Information Request  
**Importance:** High

Dear Alison,

As indicated in your e-mail below, please respond to point one of our March 27, 2012 clinical pharmacology information request by April 3, 2012. Below is a revised information request regarding the second second point of the original request. We request a response by 5 PM (EST) on April 9, 2012.

2. The correct study that needed PK parameter unit changes is study PX-171-002, the dose escalation study. Please provide the following:
  - a. The PK parameters for the PX-171-002 should be determined using clearance units of L/hr. Therefore, AUC units should be in ng•hr/mL as opposed to ng•min/mL.
  - b. Conduct and submit dose proportionality assessment using study PX-171-002 data PK parameters (AUC and Cmax). Your assessment should include all dose levels (0.6 to 27 mg/m<sup>2</sup>) where observable carfilzomib plasma concentrations are available.

All data should be provided in sas transport format.

Please acknowledge receipt of this e-mail.

Kind regards,

**KAREN BENGTON**

Regulatory Project Manager

DHP/OHOP/CDER/FDA

WO22, Room 2189

Phone: 301-796-3338

Fax: 301-796-9845

E-mail: karen.bengtson@fda.hhs.gov

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**From:** Alison Cole [mailto:acole@onyx.com]  
**Sent:** Tuesday, March 27, 2012 9:37 PM  
**To:** Bengtson, Karen  
**Cc:** Ruben Sanchez; Sheldon Mullins; John Bedard  
**Subject:** RE: NDA 202714 (Carfilzomib) - Clinical Pharmacology Information Request

Dear Karen,

Please see comments below in response to the Clinical Pharmacology Information Request sent to Onyx today, February 27<sup>th</sup>.

### Clinical Pharmacology

**“Provide simulated AUC and Cmax values following cycle 2 carfilzomib doses of 27 mg/m<sup>2</sup> (C2D15), in a manner similar to what is reported dataset in “exp-c1d1.xpt” based on your final population PK model.”**

- Due to vendor constraints, Onyx will not be able to submit simulated AUC and Cmax values analysis by tomorrow, March 28<sup>th</sup>. We anticipate that we will be able to send the values to you by next Tuesday, April 3<sup>rd</sup>. We are actively working with the vendor to expedite the availability of this analysis.

**“To facilitate inter-study PK comparison, provide PK parameters for the renal impairment study (PX-171-005) determined using clearance units of L/hr. Therefore, AUC units should be in ng•hr/mL as opposed to ng•min/mL.”**

- We went back to the CSR and PK dataset for study PX-171-005 and confirmed that the AUC units are reported in ng•hr/mL. Can FDA further clarify the request?

Please do not hesitate to email or call me if you need any additional information.

Kind Regards,  
Alison

### **Alison T. Cole**

Senior Director | Regulatory Affairs  
Onyx Pharmaceuticals Inc | 249 E. Grand Ave., | South San Francisco | CA 94080  
direct: 650.266.1672  
cell: 510.289.8523  
[acole@onyx-pharm.com](mailto:acole@onyx-pharm.com)

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**From:** Bengtson, Karen [<mailto:Karen.Bengtson@fda.hhs.gov>]  
**Sent:** Tuesday, March 27, 2012 8:55 AM  
**To:** Alison Cole  
**Cc:** Ruben Sanchez; Sheldon Mullins; John Bedard  
**Subject:** NDA 202714 (Carfilzomib) - Clinical Pharmacology Information Request  
**Importance:** High

Dear Ms. Cole:

Please refer to your New Drug Application (NDA) submitted September 26, 2011 (received September 27, 2011) under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carfilzomib (PR-171) for Injection.

We are reviewing your submission and have the following information requests. We request a written response by 5:00 PM (EST) on March 28, 2012 in order to continue our evaluation of your NDA.

### Clinical Pharmacology

Provide simulated AUC and Cmax values following cycle 2 carfilzomib doses of 27 mg/m<sup>2</sup> (C2D15), in a manner similar to what is reported dataset in “exp-c1d1.xpt” based on your final population PK model.

To facilitate inter-study PK comparison, provide PK parameters for the renal impairment study (PX-171-005) determined using clearance units of L/hr. Therefore, AUC units should be in ng•hr/mL as opposed to ng•min/mL.

All data should be provided in sas transport format.

Please acknowledge receipt of this e-mail correspondence.

Kind regards,

**KAREN BENGTSON**  
Regulatory Project Manager  
Division of Hematology Products  
OHOP/CDER/FDA  
WO22, Room 2189  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
Phone: 301-796-3338  
Fax: 301-796-9845  
E-mail: [karen.bengtson@fda.hhs.gov](mailto:karen.bengtson@fda.hhs.gov)

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KAREN E BENGTSON  
03/30/2012

**Bengtson, Karen**

---

**From:** Bengtson, Karen  
**Sent:** Tuesday, March 27, 2012 11:55 AM  
**To:** 'Alison Cole'  
**Cc:** Ruben Sanchez; Sheldon Mullins; John Bedard  
**Subject:** NDA 202714 (Carfilzomib) - Clinical Pharmacology Information Request

**Importance:** High

Dear Ms. Cole:

Please refer to your New Drug Application (NDA) submitted September 26, 2011 (received September 27, 2011) under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carfilzomib (PR-171) for Injection.

We are reviewing your submission and have the following information requests. We request a written response by 5:00 PM (EST) on March 28, 2012 in order to continue our evaluation of your NDA.

Clinical Pharmacology

1. Provide simulated AUC and Cmax values following cycle 2 carfilzomib doses of 27 mg/m<sup>2</sup> (C2D15), in a manner similar to what is reported dataset in "exp-cld1.xpt" based on your final population PK model.
2. To facilitate inter-study PK comparison, provide PK parameters for the renal impairment study (PX-171-005) determined using clearance units of L/hr. Therefore, AUC units should be in ng•hr/mL as opposed to ng•min/mL.

All data should be provided in sas transport format.

Please acknowledge receipt of this e-mail correspondence.

Kind regards,

**KAREN BENGTSON**

Regulatory Project Manager  
Division of Hematology Products  
OHOP/CDER/FDA  
WO22, Room 2189  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
Phone: 301-796-3338  
Fax: 301-796-9845  
E-mail: karen.bengtson@fda.hhs.gov

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KAREN E BENGTSON  
03/27/2012



NDA 202714

## INFORMATION REQUEST

Onyx Pharmaceuticals, Inc.  
Attention: Alison Cole  
Senior Director, Regulatory Affairs  
249 East Grand Avenue  
South San Francisco, CA 94080

Dear Ms. Cole:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carfilzomib (PR-171) for Injection.

We also refer to your February 9, 2012 submission, containing a response to an Information Request.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response via email by 5:00 PM on February 23, 2012 in order to continue our evaluation of your NDA. You will also need to follow up with a formal response to the NDA.

1. Submit safety information pertaining to patients admitted to study PX-171-007, include patients enrolled before and after amendment 2. A dataset should be submitted that allows subject level analysis for the development of cardiac, hepatic and pulmonary adverse events, one row per subject.

2. We request additional details from the following patients:

3-06-059  
3-34-811  
5-33-069  
7-23-056  
3-08-086

### For 3-06-059

The last submission from Onyx did not contain the requested data from the patient's hospitalization (Treatment Days 115 to 127). In the submitted narrative summary, the cause of death is described as *probably related to carfilzomib*. Without the requested data FDA is unable to substantiate the basis for this determination. In this submission, include:

- All hospitalization data to include:

- All vital signs,
- All hemodynamic parameters,
- Urine output,
- All lab results (including chemistry, hematology, fractionated bilirubin, microbiology, cultures and sensitivities),
- All medications with start and stop dates,
- All interventions performed,
- All diagnostic procedures, and
- All imaging studies.
- State if an autopsy was performed
- Autopsy report (if performed)
- Please discuss the evidence for and against the investigator's conclusion stated in the narrative that the death was due to hepatic failure due to carfilzomib

For 3-34-811

- All hospital medications with start and stop dates
- All vital signs during the period December 8-December 12, 2008 inclusive (the report that you sent us contained vitals signs for December 8-9 only.
- State if an autopsy was performed
- Autopsy report (if performed)

For 5-33-069

- A narrative summary of her case with emphasis on the episode of VOD
- All lab results (including chemistry, hematology, fractionated bilirubin, microbiology, cultures and sensitivities),
- All medications with start and stop dates,
- All interventions performed,
- All diagnostic procedures,
- All imaging studies, and
- Hepatitis B and C results
- The data submitted for this patient suggests that she was being worked up for and exhibited some values consistent with VOD and pulmonary arterial hypertension (PAH): right sided heart failure, dilation of right ventricle, diminished function of right ventricle, severe pulmonary hypertension, hepatomegaly with ascites on May 29, 2009. Please provide discuss this case in terms of the timing of the onset of the clinical manifestations of VOD and PAH in relationship of the date of initiation of carfilzomib.

For 7-23-056

- Pre-treatment baseline serology testing for Hepatitis B and C results
- Vital sign data from January 10 to February 13, 2008

- All lab results from January 10 to February 13, 2008 with a focus on Study Days 29 to 59 and after Day 59 (chemistry (including any tests for pancreatic function), hematology, fractionated bilirubin, microbiology, cultures and sensitivities)
- All medications with start and stop dates extending from before the initiation of carfilzomib (January 10, 2008 to February 13, 2008).

For 3-08-08

- All lab results (including chemistry, hematology, fractionated bilirubin, microbiology, cultures and sensitivities) starting pre-initiation of carfilzomib and continuing through his death of acute coronary syndrome,
- All medications with start and stop dates extending from the pretreatment period to his death,
- All interventions performed,
- The results of all diagnostic procedures with a focus on measurements of cardiac function and intracardiac pressures (ECHOs, Swan studies, etc) extending from the initiation of carfilzomib until his death,
- All imaging studies, and
- Hepatitis B and C results
- Vital signs from the pre-treatment period through to the time of death with a discussion of the reasons for hypotension that is referred to in paragraph 3, line 9 of the narrative
- A discussion of the evidence for and against carfilzomib as the cause of death
- A discussion of the reason for the abrupt increase of AST, ALT on the day of admission for his Grade 4 or 5 acute coronary syndrome

If you have any questions, call Karen Bengtson, Regulatory Project Manager, at (301) 796-3338.

Sincerely,

*{See appended electronic signature page}*

Mara Miller, M.A.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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MARA B MILLER  
02/16/2012



NDA 202714

**INFORMATION REQUEST**

Onyx Pharmaceuticals, Inc.  
Attention: Alison Cole  
Senior Director, Regulatory Affairs  
249 East Grand Avenue  
South San Francisco, CA 94080

Dear Ms. Cole:

Please refer to your New Drug Application (NDA) submitted September 26, 2011 (received September 27, 2011) under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carfilzomib (PR-171) for Injection.

We are reviewing your submission and have the following comments and information requests. We request a written response by 5:00 PM (EST) on February 15, 2012 in order to continue our evaluation of your NDA.

Clinical Pharmacology

In order to facilitate proper review of the population PK results,

1. Submit datasets used for the population PK modeling in comma separated (\*.csv) format.
2. Submit model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension (e.g., myfile\_ctl.txt, myfile\_out.txt).

If you have any questions, contact me at (301) 796-3338 or Karen.Bengtson@fda.hhs.gov.

Sincerely,

*{See appended electronic signature page}*

Karen Bengtson  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research



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/s/  
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KAREN E BENGTSON  
02/13/2012



NDA 202714

**INFORMATION REQUEST**

Onyx Pharmaceuticals, Inc.  
Attention: Alison Cole  
Senior Director, Regulatory Affairs  
249 East Grand Avenue  
South San Francisco, CA 94080

Dear Ms. Cole:

Please refer to your New Drug Application (NDA) submitted September 26, 2011 (received September 27, 2011) under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carfilzomib (PR-171) for Injection

We also refer to your January 30, 2012 submission, containing your responses to our January 10, 2012 request for information.

We are reviewing your submission and have the following information requests. We request a written response by 5:00 PM (EST) on February 8, 2012 in order to continue our evaluation of your NDA.

CLINICAL

1. We request the additional information shown below for the following patients:

- 3-06-059
- 3-08-086
- 3-08-091
- 3-32-827
- 5-33-069
- 7-23-056
- 7-30-130

All outpatient lab results.

All lab results from all hospitalizations to include vital signs, hemodynamic parameters, urine output, all lab results (including chemistry, hematology, fractionated bilirubin, microbiology, cultures and sensitivities), all medications, all interventions performed, all diagnostic procedures, all imaging studies.

2. For patient 3-34-811:

Are there positive culture results to support the diagnosis of sepsis? During this patient's hospitalization was there at any time a systolic BP less than or equal to 90 mmHg? Provide this and any clinical data that supports that the patient had shock.

If you have any questions, contact me at (301) 796-3338 or Karen.Bengtson@fda.hhs.gov.

Sincerely,

*{See appended electronic signature page}*

Karen Bengtson  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Research and Evaluation

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/s/  
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KAREN E BENGTSON  
02/03/2012



NDA 202714

**INFORMATION REQUEST**

Onyx Pharmaceuticals, Inc.  
Attention: Alison Cole  
Senior Director, Regulatory Affairs  
249 East Grand Avenue  
South San Francisco, CA 94080

Dear Ms. Cole:

Please refer to your New Drug Application (NDA) submitted September 26, 2011 (received September 27, 2011) under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carfilzomib (PR-171) for Injection.

We also refer to your submissions dated December 12, 2011 and December 16, 2011, containing your response to our request for information to evaluate hepatotoxicity and your Application Orientation presentation held on January 9, 2012.

We are reviewing your submission and have the following information requests. We request a written response by 5:00 PM (EST) on January 25, 2012 in order to continue our evaluation of your NDA.

CLINICAL

We request the following:

- The patient ID numbers for the patients that you reported were classified by (b) (4) as probably (1) and possibly (3) related drug-induced liver injury patients.
- The report on Drug Induced Liver Injury Analysis developed by (b) (4) for your company.
- Additional details from the hospitalization of patient 3-34-811 including for every day of the hospitalization leading to her death following her presentation to the ER with signs of pneumonia and hepatotoxicity: vital signs, hemodynamic parameters, urine output, all lab results (including chemistry, hematology, fractionated bilirubin, microbiology, cultures and sensitivities), all medications, all interventions performed, all diagnostic procedures, all imaging studies.

If you have any questions, contact me at (301) 796-3338 or Karen. Bengtson@fda.hhs.gov.

Sincerely,

*{See appended electronic signature page}*

Karen Bengtson  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Research and Evaluation

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KAREN E BENGTSON  
01/20/2012

## Bengtson, Karen

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**From:** Alison Cole [acole@onyx-pharm.com]  
**Sent:** Tuesday, January 10, 2012 6:13 PM  
**To:** Bengtson, Karen  
**Cc:** Sheldon Mullins; John Bedard; Alison Cole  
**Subject:** Onyx Regulatory Affairs Contact for Carfilzomib

Clarification: primary Regulatory Affairs contact for Carfilzomib project only

Kind Regards,  
Alison

---

**From:** Alison Cole  
**Sent:** Tuesday, January 10, 2012 3:11 PM  
**To:** 'Bengtson, Karen'  
**Cc:** Sheldon Mullins; John Bedard  
**Subject:** Onyx Regulatory Affairs Contact for Carfilzomib

Dear Karen

The purpose of this e-mail is to inform you that I will replace Sheldon Mullins as the primary Regulatory Affairs contact at Onyx Pharmaceuticals. Please let me know if you would like us to follow up with a formal letter.

Kind Regards,  
Alison

**Alison T. Cole**

Senior Director | Regulatory Affairs  
Onyx Pharmaceuticals Inc | 249 E. Grand Ave., | South San Francisco | CA 94080  
direct: 650.266.1672  
cell: 510.289.8523  
[acole@onyx-pharm.com](mailto:acole@onyx-pharm.com)



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KAREN E BENGTSON  
01/19/2012



NDA 202714

**INFORMATION REQUEST**

Onyx Pharmaceuticals, Inc.  
Attention: Sheldon Mullins  
Senior Director, Regulatory Affairs  
249 East Grand Avenue  
South San Francisco, CA 94080

Dear Mr. Mullins:

Please refer to your New Drug Application (NDA) submitted September 26, 2011 (received September 27, 2011) under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carfilzomib (PR-171) for Injection.

We are reviewing your submission and have the following information request. We request a prompt written response by 5:00 PM (EST) on January 30, 2012 in order to continue our evaluation of your NDA.

CLINICAL

As a follow-up to your Applicant Orientation Presentation that occurred on January 9, 2012, we request the following information:

- Any data to which you may have access showing that patients with multiple myeloma who are deemed “double resistant” (exposed to and failed a proteasome inhibitor and an IMiD) display a “negligible” response rate to therapy based on an anthracycline (e.g. Doxil) or an alkylating agent.
- Data from the medical literature or from your own experience showing that the overall response rate (ORR) in patients with relapsed/refractory multiple myeloma, who are “double resistant” (exposed to and failed a proteasome inhibitor and an IMiD) predicts overall survival (OS).
- Any additional follow-up efficacy data which may inform as to duration of remission for each of the patients enrolled in Study PX-171-003A1 who were originally classified responders to carfilzomib (PR or better) for the period between the original data lock for the NDA submission (February, 2011) and October, 2011.
- The report on Drug Induced Liver Injury Analysis by (b) (4)
- The expected 120-day safety update

If you have any questions, contact me at (301) 796-3338 or Karen.Bengtson@fda.hhs.gov.

Sincerely,

*{See appended electronic signature page}*

Karen Bengtson  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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KAREN E BENGTSON  
01/10/2012

**Bengtson, Karen**

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**From:** Ruben Sanchez [rsanchez@onyx-pharm.com]  
**Sent:** Friday, January 06, 2012 3:40 AM  
**To:** Bengtson, Karen  
**Cc:** John Bedard; Sheldon Mullins  
**Subject:** NDA 202714 Carfilzomib Application Orientation Meeting  
**Follow Up Flag:** Follow up  
**Flag Status:** Completed  
**Attachments:** CFZ\_FDA OHOP\_9Jan2012\_Full\_SlideDeck.FINALv.pdf; CFZ\_FDA OHOP\_9Jan2012\_PresentationDeck.FINALv.pdf

Hi Karen,

We have attached 2 slide decks:

- The Full Deck addresses all of the OHOP guideline topics and includes a total of 66 slides. Note that this deck also includes the answers to the 6 clinical questions sent to Onyx by FDA on November 9, 2011.
- The Presentation Deck includes the slides that Onyx will present to FDA this coming Monday, January 9<sup>th</sup> and includes a total of 52 slides (slides 1-36 composes the core of the presentation and slides 37-52 are the answers to the 6 questions to sent to Onyx by FDA on Nov 9 which are also in the full deck). All of the slides in this deck focus on clinical topics.

We would also like to ask FDA for Question #5 from November 9, 2011 if we should provide the exposure and resistance data by the six therapy classes (PI, IMiD, alkylators, anthracyclines, corticosteroids and nitrosureas). In our answer we present the data by approved agents which covers sub-classes of the aforementioned main 6 classes.

If you have any questions please let me know.

Regards,  
Ruben

Ruben Sanchez  
Associate Director  
Regulatory Affairs  
Onyx Pharmaceuticals  
T: 650-266-2572  
C: 510-590-1700  
rsanchez@onyx-pharm.com

126 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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KAREN E BENGTSON  
01/10/2012



NDA 202714

**INFORMATION REQUEST**

Onyx Pharmaceuticals, Inc.  
Attention: Sheldon Mullins  
Senior Director, Regulatory Affairs  
249 East Grand Avenue  
South San Francisco, CA 94080

Dear Mr. Mullins:

Please refer to your New Drug Application (NDA) submitted September 26, 2011 (received September 27, 2011) under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carfilzomib (PR-171) for Injection, 60 mg/vial.

We also refer to your amendments dated December 13, 2011 and December 16, 2011, containing your response to our request for information to evaluate hepatotoxicity.

We are reviewing your submission and have the following information request. We request a written response by 5:00 PM (EST) on January 6, 2012 in order to continue our evaluation of your NDA.

**CLINICAL**

In your submissions from December 13, 2011 and December 16, 2011, it is not clear what studies the submitted STUDYIDs are referencing. Submit information to indicate what study in the NDA submission corresponds to the unique STUDYIDs submitted in the submissions of December 13, 2011 and December 16, 2011. This can be accomplished by completing Column 2 of the following table.

<b>STUDYID</b>	<b>Actual Study ID in the NDA submission</b>	<b>TRTCD</b>	<b>TRTGRP</b>
1		1	1.2 mg/m2
1		2	2.4 mg/m2
1		3	4 mg/m2
1		4	6 mg/m2
1		5	8.4 mg/m2
1		6	11 mg/m2
1		7	15 mg/m2
1		8	20 mg/m2
2		1	1.2 mg/m2
2		2	2.4 mg/m2
2		3	4 mg/m2
2		4	6 mg/m2

STUDYID	Actual Study ID in the NDA submission	TRTCD	TRTGRP
2		5	8.4 mg/m2
2		6	11 mg/m2
2		7	15 mg/m2
2		8	20 mg/m2
2		9	20/27 mg/m2
2		9	20/27 mg/m2 +DEX
2		10	27 mg/m2
4		1	20 mg/m2
4		2	20/27 mg/m2
5		1	15/20/27 mg/m2
5		3	15 mg/m2
5		4	15/20 mg/m2
6		7	CFZ 15 mg/m2 LEN 10 mg DEX 40 mg
6		7	CFZ 15 mg/m2 LEN 15 mg DEX 40 mg
6		7	CFZ 15 mg/m2 LEN 20 mg DEX 4 mg
6		7	CFZ 15 mg/m2 LEN 20 mg DEX 40 mg
6		8	CFZ 20 mg/m2 LEN 20 mg DEX 4 mg
6		8	CFZ 20 mg/m2 LEN 20 mg DEX 40 mg
6		8	CFZ 20 mg/m2 LEN 25 mg DEX 40 mg
6		8	CFZ 20 mg/m2 LEN 30 mg DEX 40 mg
6		9	CFZ 20/27 mg/m2 LEN 20 mg DEX 20 mg
6		9	CFZ 20/27 mg/m2 LEN 20 mg DEX 40 mg
6		9	CFZ 20/27 mg/m2 LEN 25 mg DEX 40 mg
7		8	20 mg/m2
7		9	20/27 mg/m2
7		11	20/36 mg/m2
7		12	20/45 mg/m2
7		13	20/56 mg/m2
7		14	36 mg/m2
7		15	45 mg/m2
30		1	20 mg/m2
30		2	20/27 mg/m2
31		1	20 mg/m2
31		2	20/27 mg/m2

If you have any questions, contact me at (301) 796-3338 or Karen.Bengtson@fda.hhs.gov.

Sincerely,

*{See appended electronic signature page}*

Karen Bengtson  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research



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KAREN E BENGTSON  
01/03/2012



NDA 202714

**INFORMATION REQUEST**

Onyx Pharmaceuticals, Inc.  
Attention: Sheldon Mullins  
Senior Director, Regulatory Affairs  
249 East Grand Avenue  
South San Francisco, CA 94080

Dear Mr. Mullins:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carfilzomib (PR-171) for Injection, 60 mg/vial.

We are reviewing your submission and have the following information request. We request a written response by 5:00 PM (EST), January 23, 2012 in order to continue our evaluation of your NDA.

**Clinical**

Assess your entire Phase I and Phase II dataset for patients (with and without multiple myeloma) and provide the following information for those patients for whom such data is available:

1. Baseline and follow-up echo, pulmonary function tests, and chest imaging with an assessment of the changes between baseline and follow-up
2. Any echo results on all patients on-therapy to assess the incidence of echocardiographic diagnosis of pulmonary hypertension. Additionally, provide an assessment of how many of the patients with pulmonary hypertension were symptomatic.
3. Any pulmonary function test result of patients on-therapy, and if possible, correlate the results with the echocardiographic findings.

The file should be submitted in JMP format. Provide define files with the submission.

If you have any questions, contact me at (301) 796-3338 or Karen.Bengtson@fda.hhs.gov.

Sincerely,

*{See appended electronic signature page}*

Karen Bengtson  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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KAREN E BENGTSON  
12/22/2011



NDA 202714

**METHODS VALIDATION  
MATERIALS RECEIVED**

Onyx Pharmaceuticals, Inc.  
Attention: Sheldon Mullins  
Senior Director, Regulatory Affairs  
249 E. Grand Avenue  
South San Francisco, CA 94080

Dear Sheldon Mullins:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Carfilzomib for Injection, 60 mg/vial and to our 11/29/2011, letter requesting sample materials for methods validation testing.

We acknowledge receipt on 12/21/2011, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

James F. Allgire  
Team Leader  
Division of Pharmaceutical Analysis, HFD-920  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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JAMES F ALLGIRE  
12/21/2011



NDA 202714

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Onyx Pharmaceuticals, Inc.  
249 E. Grand Avenue  
South San Francisco, California 94080

ATTENTION: John Bedard  
Vice President, Regulatory Affairs

Dear Mr. Bedard:

Please refer to your New Drug Application (NDA) dated September 27, 2011, received September 27, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carfilzomib for Injection, 60 mg/vial.

We also refer to your September 27, 2011, correspondence, received September 27, 2011, requesting review of your proposed proprietary name, Kyprolis. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Kyprolis will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If any of the proposed product characteristics as stated in your September 27, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sue Kang, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4216. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Karen Bengtson at (301) 796-3338.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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CAROL A HOLQUIST  
12/15/2011

## Bengtson, Karen

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**From:** Bengtson, Karen  
**Sent:** Thursday, December 08, 2011 2:05 PM  
**To:** 'Sheldon Mullins'  
**Subject:** NDA 202714 (Carfilzomib) - Information Request

Dear Sheldon,

In reference to NDA 202714 for Carfilzomib (PR-171) for injection. We have the following request for information. Please provide your response as soon as possible via e-mail. If submission of datasets is required, follow with a formal submission to the NDA.

- We could not locate useful ECG dataset under study PX-171-005. Study PX-171-005 report claims ECG results are reported in TR-0480-171, but we could not locate TR-0480-171 dataset folder. Either provide the exact location of the datasets in the NDA or submit useful ECG-related datasets to TR-0480-171.

Thank you,

Karen

**KAREN BENGTSON**  
Regulatory Project Manager  
Division of Hematology Products  
OHOP/CDER/FDA  
WO22, Room 2189  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
Phone: 301-796-3338  
Fax: 301-796-9845  
E-mail: karen.bengtson@fda.hhs.gov

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KAREN E BENGTSON  
12/14/2011



NDA 202714

**FILING COMMUNICATION**

Onyx Pharmaceuticals, Inc.  
Attention: John Bedard  
Vice President, Regulatory Affairs  
249 East Grand Avenue  
South San Francisco, CA 94080

Dear Mr. Bedard:

Please refer to your New Drug Application (NDA) dated September 26, 2011, received September 27, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carfilzomib (PR-171) for Injection, 60 mg/vial.

We also refer to your amendment(s) dated November 18, 2011.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is July 27, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 8, 2012.

During our filing review of your application, we identified the following potential review issues:

Clinical

1. The primary efficacy study (PX-171-003-A1) submitted in the NDA to support your request for accelerated approval was a single-arm Phase II trial. Please be advised that recent ODAC recommendations specify a preference for Phase III trials for the accelerated approval pathway.

2. The results of this trial, as measured by the primary endpoint (our analysis indicates ORR=20.5%), do not appear to define an advantage over all approved agents for multiple myeloma.
3. The majority of the patients entered onto this Phase II trial had not been exposed to and documented to be resistant to all agents approved by FDA for myeloma. In fact, only 43 of the 266 patients entered onto the trial had been documented to be resistant to all approved agents (excluding carmustine). The FDA has requested additional information concerning this issue, which you have provided. This information, which bears on your request for an accelerated approval, is currently under review.
4. In regards to your request for accelerated approval, it is not clear from the data provided by you in the NDA or subsequently, that carfilzomib fulfills the accelerated approval criterion of filling an unmet medical need, and provides an advantage over all approved agents for this disease.
5. In our initial review of your application, a significant hepatotoxicity signal was noted. Three on-study deaths were attributed to acute hepatotoxicity, and 12% of myeloma patients on Phase I and II trials experienced dose reductions of carfilzomib due to elevations of AST. Across all trials, 12% of patients in the ISS experienced elevations of AST, 3% of which were Grade 3 or greater and 2% of patients experienced grade 3 elevations of bilirubin. The FDA has already sent to you an information request (#3) for additional information on these patients.
6. In our initial review of your application, a significant cardiac safety signal was noted. In study, PX-171-003, 60 subjects (22.6%) developed a cardiac adverse event. There were seven cardiac events with death reported as the outcome. In five of these seven deaths, the event occurred while on study drug. There was also a 6% incidence for the grouped cardiac failure term, which included events of congestive cardiac failure, pulmonary edema, decreased ejection fraction, cardiac failure and acute pulmonary edema. Additionally, there were several cases of pulmonary hypertension. This issue is currently under review and the FDA may be requesting additional information about cardiopulmonary adverse events in the future.

#### Microbiology

7. Reference is made to Section 2.6 (*Reconstitution and Preparation for Intravenous Administration*) of the draft label. The following comment is provided in response to your plan to allow a (b) (4) holding time at room temperature between reconstitution of the drug product and patient administration:

Provide microbiological data in the NDA to demonstrate that the reconstituted product solution will not support microbial growth during the proposed storage period at room temperature. Provide a risk assessment summarizing studies that show adventitious microbial contamination does not grow under the storage conditions. Reference is made to the *Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E* and *Guidance*

*for Industry: ICH Q1A (R2) Stability Testing of New Drug Substances and Products, Section 2.2.7.*

Generally, “no growth” is interpreted as not more than 0.5 log<sub>10</sub> increase from the initial count; however, other evidence of growth may be significant. The test should be run at the label’s recommended storage conditions, be conducted two to three times the label’s recommended storage period, and use the label-recommended fluids inoculated with low numbers ( $\leq 100$  CFU/mL) of challenge microbes. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with the hospital-borne infections. In lieu of these data, the product labeling should be amended to recommend that the post-constitution storage period is not more than 4 hours at room temperature or 24 hours at refrigerated temperature.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. The Highlights page should be in the portrait orientation, not landscape. Change the orientation of this page and ensure that the Highlights do not exceed one-half page of standard-sized paper (8 ½ by 11 in.), in 8-point type, two-column format [see 21 CFR 201.57(d)(8)].
2. Ensure that white space precedes each major heading in the Highlights section.
3. Each summarized statement in the Highlights must cross-reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information.
  - Add the cross-reference to the second bullet point under “Dosage and Administration.”
4. The Warnings and Precautions (WPs) in the Highlights should be listed in the same order as the WPs in the FPI section.
  - List (b) (4) before (b) (4)
5. The Revision Date for the most recent revision of the labeling, identified as such, must be placed at the end of the Highlights [see 21CFR 201.57(a)(15)]. For new applications, the revision date will be the month/year of application approval.
  - Add the revision date to the end of the Highlights in one of the following formats using bold font: "Revised: Month Year" or "Revised Month/Year" (e.g., Revised: Month YEAR or Revised MM/YYYY).

6. The revision date at the end of Highlights replaces the “revision” or “issued” date at the end of the FPI and should not appear in both places.
  - Delete “Issued: [Date of Approval]” from the end of FPI.
7. You should remove the underline under the heading “Full Prescribing Information” shown at beginning of FPI section. The title must appear in UPPER CASE and bold type only.
8. The section headings and subheadings in the FPI: Contents must match the headings and subheadings in the FPI.
  - The subheading listed for 2.4 does not match the FPI. They are listed as “Dose Modification” and “Dose Modifications,” respectively. Resolve this discrepancy.
9. A horizontal line is required that separates the “Full Prescribing Information: Contents” and the” Full Prescribing Information” (FPI) [*see 21 CFR 201.57(d)(2)*]. Add this horizontal line to the labeling.
10. The presentation for cross-references in the FPI should be the section heading followed by the numerical identifier. For example, instead of [*see Dose Modifications (2.4)*] the cross-reference should be presented as [*see Dosage and Administration (2.4)*]. Do not include the subsection headings or other headings within a subsection in the cross-references. Update cross-references within the FPI accordingly.

We request that you resubmit labeling that addresses these issues by December 30, 2011. The resubmitted labeling will be used for further labeling discussions.

Please respond only where additional information has been requested. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

#### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, contact Karen Bengtson, Regulatory Project Manager, at (301) 796-3338.

Sincerely,

*{See appended electronic signature page}*

Ann T. Farrell, M.D.  
Acting Director  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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ANN T FARRELL  
12/08/2011



NDA 202714

**REQUEST FOR METHODS  
VALIDATION MATERIALS**

Onyx Pharmaceuticals, Inc.  
Attention: Sheldon Mullins  
Senior Director, Regulatory Affairs  
249 E. Grand Avenue  
South San Francisco, CA 94080

Dear Mr. Sheldon Mullins:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Carfilzomib for Injection, 60 mg/vial.

We will be performing methods validation studies on Carfilzomib for Injection, 60 mg/vial, as described in NDA 202714

In order to perform the necessary testing, we request the following sample materials and equipments:

**CURRENT METHODS**

(b) (4) Identification, Assay and Impurities  
(b) (4) Assay and Related Substances  
(b) (4) Identification

**SAMPLE**

250 mg Carfilzomib Drug Substance  
12 vials Carfilzomib for injection, 60 mg/vial

**REFERENCE MATERIALS**

250 mg Carfilzomib  
50 mg (b) (4)  
50 mg  
50 mg  
50 mg  
50 mg  
50 mg  
50 mg  
50 mg  
50 mg  
30 g Captisol



COLUMN

1

(b) (4)

Please include the MSDSs and Certificates of Analysis for the samples and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration  
Division of Pharmaceutical Analysis  
Attn: James F. Allgire  
1114 Market Street, Room 1002  
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

James F. Allgire  
Team Leader  
Division of Pharmaceutical Analysis, HFD-920  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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JAMES F ALLGIRE  
11/29/2011

## Bengtson, Karen

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**From:** Bengtson, Karen  
**Sent:** Monday, November 28, 2011 4:35 PM  
**To:** 'Sheldon Mullins'  
**Cc:** John Bedard  
**Subject:** NDA 202714 - Clinical Pharmacology Information Request

**Importance:** High

**Attachments:** HighlightsofClinicalPharmacology.doc

Dear Sheldon:

Please refer to your New Drug Application (NDA) dated September 26, 2011 (received September 27, 2011) under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carfilzomib (PR-171) for Injection. We have the following request for additional information. Please provide your response via e-mail as soon as possible and follow with a formal submission to the NDA.

### Clinical Pharmacology

- Complete the information in the attached Clinical Pharmacology table.



HighlightsofClinicalP  
armacolo...

Please acknowledge receipt of this e-mail correspondence.

Kind regards,

**KAREN BENGTSON**

Regulatory Project Manager  
Division of Hematology Products  
OHOP/CDER/FDA  
WO22, Room 2189  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
Phone: 301-796-3338  
Fax: 301-796-9845  
E-mail: karen.bengtson@fda.hhs.gov

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## Highlights of Clinical Pharmacology

Therapeutic dose	Include maximum proposed clinical dosing regimen.	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	<ul style="list-style-type: none"> <li>Median (range) for parent</li> <li>Median (range) for metabolites</li> </ul>
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> <li>Primary route; percent dose eliminated</li> <li>Other routes</li> </ul>
	Terminal t <sub>1/2</sub>	<ul style="list-style-type: none"> <li>Mean (%CV) for parent</li> <li>Mean (%CV) for metabolites</li> </ul>
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	

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/s/  
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KAREN E BENGTSON  
11/29/2011



NDA 202714

**INFORMATION REQUEST**

Onyx Pharmaceuticals, Inc.  
Attention: John Bedard  
Vice President, Regulatory Affairs  
249 East Grand Avenue  
South San Francisco, CA 94080

Dear Mr. Bedard:

Please refer to your New Drug Application (NDA) submitted September 26, 2011, received September 27, 2011, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carfilzomib (PR-171) for Injection, 60 mg/vial.

We are reviewing the clinical section of your submission and have the following comments and information requests. We request a written response by 5 PM, December 12, 2011 in order to continue our evaluation of your NDA.

**CLINICAL**

**1. Detailed Listing of Laboratory Data Relevant to Hepatotoxicity in the ISS Population:**

As outlined in the ISS document that was submitted as part of NDA 202714, approximately 12% of the ISS population was observed to experience elevations of serum transaminases (see page 209 of the ISS), 3% of the ISS population experienced grade 3 or greater elevations of AST (see page 209 of the ISS), and 2% of the ISS population experienced grade 3 or greater elevations of serum total bilirubin (see page 233 of the ISS). Dose reductions due to elevations of AST were implemented in 12% of myeloma patients on the Phase II trials (see page 154 of the ISS), and 12.5% of patients experiences dose reductions due to AST elevations on the Phase I trials of myeloma patients (see page 159 of the ISS).

There were 3 on study deaths (within 30 days of the last carfilzomib administration in the ISS (patient numbers 3-06-059, 3-34-811, and 7-30-130, and 7 candidate Hy's law cases reported by you in the ISS (Table 72 on page 413 of the ISS).

On this basis, we are requesting more detained information about the profile of hepatotoxicity in your clinical studies of carfilzomib. For the entire ISS population, submit the following data as part of a SAS transport file in CDISC terms as described in the following tables.

Table 1 summarizes the requirements for the laboratory data we are requesting for hepatotoxicity. Table 2 summarizes the demographic data that we are requesting to enable us to more fully evaluate.

**Table 1: Requirements for Laboratory Data for Evaluation of Hepatotoxicity**

Requirement	Standard variable	The variable means...	Variable-type
1. <a href="#">Required</a>	STUDYID	Unique identifier for a study within the submission	Char
2. <a href="#">Required</a>	USUBJID	Unique subject identifier within the submission	Char
3. <a href="#">Required</a>	TRTCD	Treatment Code	Num
4. <a href="#">Required</a>	TRTGRP	Treatment Group	Char
5. <a href="#">Required</a>	EXSTDY	Start Date of Dose	Char (ISO 8601 YYYY-MM-DD)
6. <a href="#">Required</a>	EXDT	Date of Exam	Char (ISO 8601 YYYY-MM-DD)
7. <a href="#">Required</a>	EXENDT	End Date of Dose	Char (ISO 8601 YYYY-MM-DD)
8. <a href="#">Required</a>	ALT	Serum alanine aminotransferase activity (U/L)	Num
9. <a href="#">Required</a>	ALT_REF_HIGH	ALT High Normal Range (U/L)	Num
10. <a href="#">Required</a>	BILI	Total serum bilirubin concentration (mg/dL)	Num
11. <a href="#">Required</a>	BILI_REF_HIGH	BILI High Normal Range (mg/dL)	Num
12. <a href="#">Required</a>	AST	Serum aspartate aminotransferase (U/L)	Num
13. <a href="#">Required</a>	AST_REF_HIGH	AST High Normal Range (U/L)	Num
14. <a href="#">Required</a>	ALP	Alkaline phosphatase (U/L)	Num
15. <a href="#">Required</a>	ALP_REF_HIGH	ALP High Normal Range (U/L)	Num
16. <a href="#">Optional</a>	ONPROTOD	Subject on Protocol at the Time of exam (Y/N)	Num
17. <a href="#">Optional</a>	GGT	Gamma glutamyl transferase (U/L)	Num

**Table 2: Demographic Data Relevant to Evaluation of Hepatotoxicity**

Requirement	Standard variable	The variable means...	Variable-type
1. <a href="#">Required</a>	STUDYID	Unique identifier for a study within submission	Char
2. <a href="#">Required</a>	USUBJID	Unique subject identifier within submission	Char
3. <a href="#">Required</a>	INVID	Investigator Identifier	Char
4. <a href="#">Optional</a>	INVNAM	Investigator Name	Char
5. <a href="#">Optional</a>	INVDISC	Investigator Description	Char
6. <a href="#">Required</a>	BIRTHDT	Date of birth	Char (ISO 8601 YYYY-MM-DD)

Requirement	Standard variable	The variable means...	Variable-type
7. <a href="#">Required</a>	SEX	Sex (M/F)	Char
8. <a href="#">Optional</a>	RACE	Race (WHITE, BLACK, OTHER)	Char
9. <a href="#">Optional</a>	COUNTRY	Country	Char
10. <a href="#">Required</a>	HEIGHT	Height in cm	Num
11. <a href="#">Required</a>	WEIGHT	Weight in kg	Num
12. <a href="#">Required</a>	COMPLETE	Subject completing the study (Y/N)	Char
13. <a href="#">Required</a>	DROPDT	Date subject discontinued the study (Y/N)	Char (ISO 8601 YYYY-MM-DD)
14. <a href="#">Required</a>	DROPREAS	Reason for discontinuation	Char
15. <a href="#">Required</a>	NARRATE	Availability of Patient Narratives (Y/N)	Char

## 2. Request for Detailed Narratives for Candidate Hy's Law Cases

We are requesting more detailed narratives than were provided in the ISS document in the NDA submission of September 26, 2011 for patients reported by you to be candidate Hy's Law Cases. The requirements for these narratives are listed below in Table 3.

**Table 3: Requirements for the clinical narrative data**

Requirement	Standard variable	The variable means...	Variable-type
1. <a href="#">Required</a>	STUDYID	Unique identifier for a study within the submission	Char
2. <a href="#">Required</a>	USUBJID	Unique subject identifier within the submission	Char
3. <a href="#">Required</a>	NARRATIVE	Clinical Narrative*	Char
* Requirements for Variable NARRATIVE - To the medical writer: It is not necessary to include all subjects in this patient narrative data set. However, make sure to include narratives			

Note that only STUDYID and USUBJID are CDISC terms. The variable NARRATIVE is a character variable which can hold about 4,000 characters in a long text string.

The clinical narrative should be prepared by a physician knowledgeable about differential diagnosis to determine the likelihood that the observed finding were not caused by carfilzomib, but by disease, or other drugs or agents. It is not necessary to include all subjects in this patient narrative data set. However, make sure to include narratives for subjects with either ALT > 3xULN or TBL > 2xULN.

The narratives should include information described in the following points:

- Indication
- Subject's medical history and concomitant medications
- Dates and laboratory values of diagnostic tests done to evaluate liver disease including X-ray, ultrasound, or liver biopsy
- Time course of any signs or symptoms of liver disease, including jaundice



- e) Differential diagnosis and final diagnosis of liver disease
- f) The study site investigator and the sponsor's assessment of relationship of study drug to abnormal hepatobiliary lab results or adverse events
- g) Clinical course of liver-related adverse events including treatment and outcome
- h) Complete information about the resolution, or progression, of increased ALT or total bilirubin in each of these study subjects, including time to complete resolution of all hepatobiliary lab results, or most current available patient status for any cases in which the events had not resolved at the time of report preparation.
- i) It is also helpful to include in the narrative:
  - Dose and duration of study therapy in weeks
  - Laboratory values for ALT, AST, ALP, TBL and corresponding dates of measurements

If you have any questions, contact me at (301) 796-3338 or Karen.Bengtson@fda.hhs.gov.

Sincerely,

*{See appended electronic signature page}*

Karen Bengtson  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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KAREN E BENGTSON  
11/28/2011

## Bengtson, Karen

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**From:** Bengtson, Karen  
**Sent:** Monday, November 21, 2011 1:53 PM  
**To:** 'Sheldon Mullins'  
**Cc:** John Bedard  
**Subject:** NDA 202714 - Information Request

Dear Sheldon:

Please refer to your New Drug Application (NDA) dated September 26, 2011 (received September 27, 2011) under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carfilzomib (PR-171) for Injection. We have the following request for additional information. Please provide your response via e-mail by close of business November 25, 2011.

- For study protocol ID PX-171-003, submit patient data listings to include screening until end of study values or findings for the following: (1) serum electrophoresis, (2) urine electrophoresis, (3) soft tissue plasmacytoma findings (if any), and (4) bone marrow aspirate/biopsy findings.

Please acknowledge receipt of this e-mail correspondence.

Best regards,  
Karen

**KAREN BENGTSON**  
Regulatory Project Manager  
Division of Hematology Products  
OHOP/CDER/FDA  
WO22, Room 2189  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
Phone: 301-796-3338  
Fax: 301-796-9845  
E-mail: karen.bengtson@fda.hhs.gov

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/s/  
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KAREN E BENGTSON  
11/21/2011

## Bengtson, Karen

---

**From:** Bengtson, Karen  
**Sent:** Monday, November 14, 2011 2:07 PM  
**To:** 'Sheldon Mullins'  
**Subject:** NDA 202714 - Establishment Information on Form FDA 356h

Hello Sheldon,

All establishments and their registration numbers should be either listed on the form FDA 356h or attached to the form. I could not locate the listing of establishment on the form or as an attachment in your submission for NDA 202714. Please submit an updated form with this information as soon as possible.

Thank you,

**KAREN BENGTSON**  
Regulatory Project Manager  
Division of Hematology Products  
OHOP/CDER/FDA  
WO22, Room 2189  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
Phone: 301-796-3338  
Fax: 301-796-9845  
E-mail: karen.bengtson@fda.hhs.gov

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/s/  
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KAREN E BENGTSON  
11/14/2011



NDA 202714

**INFORMATION REQUEST**

Onyx Pharmaceuticals, Inc.  
Attention: John Bedard  
Vice President, Regulatory Affairs  
249 East Grand Avenue  
South San Francisco, CA 94080

Dear Mr. Bedard:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carfilzomib (PR-171) for Injection, 60 mg/vial.

We are reviewing the clinical section of your submission and have the following information request. We request a written response by 5 PM (EST) on November 18, 2011 in order to continue our evaluation of your NDA.

Clinical - Study PX-171-003, Part 2 (A1)

1. Submit a list of patients by patient ID who have received and have been documented to be unresponsive to or intolerant of the following agents. Submit the file in JMP format. Provide define files with the submission.
  - a) Melphalan
  - b) Cyclophosphamide
  - c) Any Anthracycline
  - d) Lenalidomide
  - e) Thalidomide
  - f) Bortezomib
  - g) Carmustine

If you have any questions, contact me at (301) 796-3338 or Karen.Bengtson@fda.hhs.gov.

Sincerely,

*{See appended electronic signature page}*

Karen Bengtson  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research



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/s/  
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KAREN E BENGTSON  
11/14/2011

## MEMORANDUM OF TELECONFERENCE MEETING MINUTES

**MEETING DATE:** November 4, 2011  
**TIME:** 4:00 PM – 4:30 PM  
**LOCATION:** WO22, Conference Room 2201  
**APPLICATION:** NDA 202714  
**DRUG NAME:** Carfilzomib (PR-171) for Injection

**MEETING CHAIR:** Albert Deisseroth, M.D.

**MEETING RECORDER:** Karen Bengtson

### **FDA ATTENDEES:**

#### OFFICE OF NEW DRUGS/OFFICE OF HEMATOLOGY AND ONCOLOGY PRODUCTS/DIVISION OF HEMATOLOGY PRODUCTS

Ann Farrell, M.D. – Director (Acting)  
Albert Deisseroth, M.D. – Clinical Team Leader (Acting)  
Thomas Herndon, M.D. – Medical Officer  
R. Angelo de Claro, M.D. – Medical Officer  
Karen Bengtson – Regulatory Project Manager

### **EXTERNAL CONSTITUENT ATTENDEES:**

#### ONYX PHARMACEUTICALS, INC. (Onyx)

John Bedard – Vice President, Regulatory Affairs  
Alison Cole – Senior Director, Product Leader  
Arthur DeVault, Ph.D. – Senior Director, Biometrics  
Barbara Klencke, M.D. – Vice President, Clinical Development  
Ted Love, M.D. – Executive Vice President, R&D and Technical Operations  
Sheldon Mullins, Senior Director, Regulatory Affairs  
Natalie Sacks, M.D. – Group Medical Leader, Clinical Sciences

### **BACKGROUND:**

Onyx Pharmaceuticals, Inc. completed their rolling submission of NDA 202714 - Carfilzomib (PR-171) for Injection - on September 26, 2011 (received September 27, 2011). Carfilzomib is a proteasome inhibitor proposed for the treatment of patients with relapsed and refractory multiple myeloma who have failed at least two prior therapies. Onyx is seeking accelerated approval for carfilzomib. On October 18, 2011, a clinical information request (IR) was sent to Onyx to determine how many of the patients entered into the pivotal phase II trial of the NDA had been exposed to and shown to be refractory or intolerant of available therapy (agents which have already been approved by the FDA for the treatment of myeloma). This information is relevant to the request by the company for accelerated approval.

On October 19, 2011, the Agency held a teleconference with Onyx to provide clarification on the information request. On October 21, 2011, Onyx requested a follow-up teleconference with DHP to address questions that arose during their compilation of the data in response to the information request.

**MEETING OBJECTIVES:**

To provide general advice/clarification regarding the Agency's expectation for accelerated approval criteria.

**DISCUSSION POINTS:**

Onyx asked if their recent IR response was adequate. FDA replied that the response was adequate, but the data needed to be submitted in SAS files. Onyx agreed to submit the data in this format.

Onyx then asked for clarification as to how the Agency defines "available therapy." The Agency stated that available therapy is defined as all of the agents for which full approval has been granted for the indication in question. This is outlined in the Guidance for Industry on Available Therapy. The Agency further stated that they must adhere to the regulations for accelerated approval which state that for a drug to be approved by the accelerated approval mechanisms, it must provide meaningful therapeutic benefit to patients over available therapy treatments in patients unresponsive to or intolerant of available therapy.

Onyx asked for clarification as to whether carmustine was included as available therapy because it is used for palliative care. The Agency recommended that Onyx present their justification as to why patients are not candidates for carmustine or why exposure to carmustine is not appropriate for these patients.

The Agency informed Onyx that the accelerated approval issue is separate from filing considerations.

**DECISIONS (AGREEMENTS) REACHED:**

N/A

**UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:**

N/A

**ACTION ITEMS:**

N/A

**ATTACHMENTS/HANDOUTS:**

N/A

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/s/  
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KAREN E BENGTSON  
11/16/2011

## MEMORANDUM OF TELECONFERENCE MEETING MINUTES

**MEETING DATE:** October 19, 2011  
**TIME:** 1:00 PM – 1:15 PM  
**LOCATION:** WO22, Conference Room 2376  
**APPLICATION:** NDA 202714  
**DRUG NAME:** Carfilzomib (PR-171) for Injection

**MEETING CHAIR:** Thomas Herndon, M.D.

**MEETING RECORDER:** Karen Bengtson, RPM

### **FDA ATTENDEES:**

#### OFFICE OF NEW DRUGS/OFFICE OF HEMATOLOGY AND ONCOLOGY PRODUCTS/DIVISION OF HEMATOLOGY PRODUCTS

Thomas Herndon, M.D. – Medical Officer  
Albert Deisseroth, M.D. – Clinical Team Leader (Acting)  
Karen Bengtson, B.A. – Regulatory Project Manager

### **EXTERNAL CONSTITUENT ATTENDEES:**

#### ONYX PHARMACEUTICALS, INC. (Onyx)

Arthur DeVault – Senior Director, Biometrics  
Alvin Wong – Senior Director, Clinical Science  
Natalie Sacks – Group Medical Leader, Clinical Science  
Alison Cole – Senior Director, Product Leader  
Michelle Pallas – Director, Statistical Programming  
Ruben Sanchez – Associate Director, Regulatory Affairs  
Sheldon Mullins – Senior Director, Regulatory Affairs  
David Cornpropst – Senior Director, Program Management

### **BACKGROUND:**

Onyx Pharmaceuticals, Inc. completed their rolling submission of NDA 202714 - Carfilzomib (PR-171) for Injection - on September 26, 2011 (received September 27, 2011). Carfilzomib is a proteasome inhibitor proposed for the treatment of patients with relapsed and refractory multiple myeloma who have failed at least two prior therapies. Onyx is seeking accelerated approval for carfilzomib. On October 18, 2011, a clinical information request was sent to Onyx requesting data demonstrating that carfilzomib has met the accelerated approval criteria (e.g. ability to treat patients unresponsive to or intolerant of available therapy). On October 18, 2011, Onyx requested a brief teleconference with Division of Hematology Products (DHP) regarding the information request.

**MEETING OBJECTIVES:**

To clarify the details of the information request and timing of Onyx's response.

**DISCUSSION POINTS:**

1. Onyx requested clarification on the details of the information request. DHP clarified that the data should be presented in two tables: one with data regarding exposure to available therapies and one showing the data demonstrating patients refractory to the available therapies. Further, DHP explained that the data should be broken down into the six major classes of drugs. (b) (4)

(b) (4) DHP clarified that for the Approved Drug Class Anthracyclines, the following sub-analyses should be performed: 1. Doxil and 2. Any anthracycline including Doxil. DHP requested Onyx also include the patient listings that correspond to the data in each table representing the available therapy category and the progression (b) (4)

2. Onyx requested that they be allowed to submit their e-mail response to the information request on Sunday, October 23, 2011 instead of the original DHP requested time/date of 5 PM (EST) on October 21, 2011. DHP agreed to the request.
3. Onyx inquired about the timing of the formal response to the NDA. DHP informed Onyx that they should submit their response as an amendment to module 5 of their NDA as soon as possible following their e-mail response, but that it was not required to be submitted on the same date.

**DECISIONS (AGREEMENTS) REACHED:**

None

**UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:**

None

**ACTION ITEMS:**

- Onyx will provide their response to the information request via e-mail to the Regulatory Project Manager on Sunday, October 23, 2011, so that it will be available to DHP for review by start of business on Monday, October 24, 2011.

**ATTACHMENTS/HANDOUTS:**

None

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/s/  
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KAREN E BENGTSON  
10/19/2011

## Bengtson, Karen

---

**From:** Bengtson, Karen  
**Sent:** Tuesday, October 18, 2011 4:44 PM  
**To:** John Bedard  
**Cc:** Sheldon Mullins  
**Subject:** NDA 202714 (Carfilzomib) - Information Request

**Importance:** High

Dear Mr. Bedard:

Please refer to your New Drug Application (NDA) dated September 26, 2011 (received September 27, 2011) under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carfilzomib (PR-171) for Injection.

We are reviewing your submission and have the following information requests. We request a written response via e-mail by **5:00 PM on October 21, 2011** in order to continue our evaluation of your NDA. You will also need to follow up with a formal response to the NDA.

### CLINICAL

Submit information to demonstrate that Carfilzomib has met the accelerated approval criteria of having exhausted available therapies. To that end, provide information on the fully approved agents and classes of agents for multiple myeloma that patients had received and failed prior to enrollment in clinical trial, PX-171-003-Part 2 (A1).

Please provide this in two tables: one that contains the number of patients exposed to the Approved Classes, and a second that contains the number of patients documented to have received and to have been shown to be refractory to the Approved Classes. The Approved Classes for the tables are: Proteasome inhibitors, IMiDs, Alkylators, Anthracyclines, Corticosteroids, and Nitrosureas.

The tables should contain information on the number of patients who received or were refractory to each treatment class (i.e., received 6, 5, 4, 3 or less of the approved classes of agents), ASCT status and the best response. See below:

Number of classes	6		5		4		≤3	
ASCT	No	Yes	No	Yes	No	Yes	No	Yes
N (%)								
Best Response								
CR								
PR (total)								
uCR								
VGPR								
PR								
MR								
SD								
PD								
NE								

In addition, provide analyses within each Class according to the U.S. approved agents. The Proteasome inhibitors should contain only Bortezomib. The IMiDs should contain the following sub-analyses: Lenalidomide only, Thalidomide only, Lenalidomide or Thalidomide, Lenalidomide and Thalidomide. Alkylators should contain the following sub-analyses: Melphalan only, Cyclophosphamide only, and Melphalan or Cyclophosphamide. Anthracyclines should contain the following sub-analyses: Doxil only, and



any anthracycline. Corticosteroids should contain Dexamethasone only, Prednisone only, and Dexamethasone or Prednisone. Nitrosureas should contain Carmustine only.

Please acknowledge receipt of the message. If you have any questions, feel free to contact me.

Best regards,

Karen

**KAREN BENGTON**

Regulatory Project Manager  
Division of Hematology Products  
OHOP/CDER/FDA  
WO22, Room 2189  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
Phone: 301-796-3338  
Fax: 301-796-9845  
E-mail: karen.bengtson@fda.hhs.gov

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/s/  
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KAREN E BENGTSON  
10/18/2011



NDA 202714

**NDA ACKNOWLEDGMENT**

Onyx Pharmaceuticals, Inc.  
Attention: John Bedard  
Vice President, Regulatory Affairs  
249 East Grand Avenue  
South San Francisco, CA 94080

Dear Mr. Bedard:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Carfilzomib (PR-171) for Injection, 60 mg/vial

Date of Application: September 26, 2011

Date of Receipt: September 27, 2011

Our Reference Number: NDA 202714

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 26, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Hematology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, contact Karen Bengtson, Regulatory Project Manager, at (301) 796- 3338 or [Karen.Bengtson@fda.hhs.gov](mailto:Karen.Bengtson@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Janet Jamison, RN, CCRP  
Chief, Project Management Staff  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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JANET K JAMISON  
10/06/2011



NDA 202714

**ACKNOWLEDGE CORPORATE  
NAME/ADDRESS CHANGE**

Onyx Pharmaceuticals, Inc.  
Attention: John Bedard  
Vice President, Regulatory Affairs  
249 East Grand Avenue  
South San Francisco, CA 94080

Dear Mr. Bedard:

We acknowledge receipt on September 27, 2011, of your September 26, 2011 correspondence notifying the Food and Drug Administration that the corporate name and/or address has been changed from

Onyx Pharmaceuticals, Inc.  
2100 Powell Street  
Emeryville, CA 94608

to

Onyx Pharmaceuticals, Inc.  
249 East Grand Avenue  
South San Francisco, CA 94080

for the following new drug application:

NDA 202714 for Carfilzomib (PR-171) for Injection, 60 mg/vial.

We have revised our records to reflect this change.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Hematology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions, contact me at (301) 796-3338 or [Karen.Bengtson@fda.hhs.gov](mailto:Karen.Bengtson@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Karen Bengtson  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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KAREN E BENGTON  
10/05/2011





**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA (CMC)  
  
**Meeting Date and Time:** Tuesday, September 28, 2010 10:00 – 11:00 AM, EST  
**Meeting Location:** FDA White Oak Building 22 Room 1415  
  
**Application Number:** IND 071057  
**Product Name:** PR-171 (carfilzomib) Injection  
**Indication:** for the treatment of hematological malignancies  
**Sponsor/Applicant Name:** Onyx Therapeutics Inc.  
  
**Meeting Chair:** Sarah Pope Miksinski, Ph.D.  
**Meeting Recorder:** Tu-Van Le Lambert, M.S.

**FDA ATTENDEES**

Sarah Pope Miksinski, Ph.D. – Chief, Branch II, Division of New Drug Quality Assessment I (DNDQA I), Office of New Drug Quality Assessment (ONDQA)  
Janice T. Brown, M.S. – CMC Lead, DNDQA I, ONDQA  
Anne Marie Russell, Ph.D. – Product Quality Reviewer, Branch II, DNDQA I, ONDQA  
Albert Deisseroth, M.D. – Medical Officer, Division of Hematology Products, Office of Oncology Drug Products  
Tu-Van Le Lambert, M.S. – Product Quality Regulatory Project Manager, DNDQA I, ONDQA

**SPONSOR ATTENDEES**

Linda Yokoshima - Associate Director, Regulatory Affairs, Onyx  
Sean Dalziel, Ph.D. - Senior Director, Technical Operations, Onyx  
Pasit Phiasivongsa, Ph.D. - Associate Director, Chemical Development, Onyx  
Mouhannad Jumaa, Ph.D. - Senior Scientist, Pharmaceutical Development, Onyx  
Nazila Habibizad - Associate Director, Analytical Development, Onyx  
John McGinley - Associate Director, Quality Assurance, Onyx  
Albert Kraus, Ph.D. - Transition Executive, Senior Drug Development Advisor, Onyx  
Alison Cole - Senior Director, Carfilzomib Project Team Leader, Onyx

(b) (4)



## 1.0 BACKGROUND

This IND, originally submitted on June 13, 2005, provides for an indication for the treatment of hematological malignancies. The meeting request reference an End of Phase 2 meeting with the Agency held on August 3, 2009. During this EOP2 meeting, the Agency made comments and recommendations regarding the drug substance and drug product manufacturing development plan. The Sponsor intends to provide follow-up information in addressing these comments. These comments are related to the proposed two starting materials for the drug substance, including re-designation of the starting materials, its manufacturing process (with a transfer of the starting material manufacturer), and the analytical test methods and acceptance criteria.

## 2. DISCUSSION

Preliminary responses from the Agency were sent on September 23, 2010. Based on these preliminary responses, the Sponsor requested further discussions of Agency comments Questions 1a, 2c, 5 and 7. These questions are included in the discussion below. Questions provided by the Sponsor are in ***Bold Italics***, FDA Responses provided in preliminary comments are in Regular, discussion items during the meeting are in *Italics*.

On September 27, 2010, the Sponsor submitted additional information to address the Agency's preliminary responses (see Appendix 1). This information, which included new data and analyses, was not reviewed for this meeting as it was not included in the initial meeting package with sufficient time for review.

### 2.1 DRUG SUBSTANCE

***QUESTION 1: Does the FDA agree that drug substance manufactured by (b) (4) using the newly designated starting material, (b) (4) produced at (b) (4) is suitable for NDA submission and commercialization?***

**FDA Response:**

No, there was insufficient information available in your meeting package to evaluate the quality of the drug substance manufactured using the intended commercial process since the batch data for only a single lot (b) (4) was submitted. Data was not provided for any lots of drug substance that were manufactured using (b) (4) produced at (b) (4).

We have some comments regarding the supporting data submitted for question 1.

Drug substance:

- a. Drug substance lot (b) (4) is notably different than historical clinical lots manufactured before the process change was implemented - including impurities, specific rotation and residual solvents. Due to these differences, a minimum of three lots of drug substance manufactured using the intended commercial process will be needed to support an NDA submission. Historical lots can be submitted as supportive data. However, NDA review will be based on batches produced by the proposed commercial process.

- b. Conduct Phase 3 clinical trials with the drug product manufactured using the intended commercial process.

Intermediate (b) (4)

- c. For new lot (b) (4) of the intermediate (b) (4)

(b) (4) Batch Summary (Table 2) when comparing the HPLC data from the (b) (4) new lot to the (b) (4) historical lots. This indicates that the historical (b) (4) HPLC method and the new (b) (4) HPLC method may not generate comparable data, or that new impurities are generated in the intended commercial process. Consequently, the historical data cannot provide a reference for the new data to demonstrate the continuity of the quality of (b) (4) on transfer from (b) (4) to (b) (4). Provide data to support that there are no new impurities (listed above) in the intended commercial process.

**Sponsor reply to FDA response:**

- 1a. See attached "Response to FDA Preliminary Pre-NDA CMC Meeting Questions" in Appendix 1.
- 1b. Onyx will include drug product using the intended drug substance commercial process in the ongoing Phase 3 trial (PX-1717-009).
- 1c. See attached "Response to FDA Preliminary Pre-NDA CMC Meeting Questions" in Appendix 1.

**Discussion:**

***1a.***

- The Sponsor clarified that one lot of drug substance has been manufactured by the intended commercial process from starting material (b) (4) supplied by (b) (4). They notified the agency that the drug substance will not be manufactured using (b) (4) produced at (b) (4) will be the only supplier of (b) (4).*
- In their presentation, the Sponsor provided new data (specific rotation, residual solvents, impurities and manufacturing process) on their lot of drug substance manufactured by the intended commercial process. They proposed that this commercial batch was within the uncertainty range of their historical data despite the values being outside the reported historical data. When asked if this data was acceptable, the Agency responded that this information was not provided for review in the initial meeting package and no comments could be made at this time. The acceptability of this data would be a review issue. The Sponsor accepted this response.*
- The Agency emphasized that their NDA should include complete characterization of the desired product and impurities that are present at levels greater than the identification threshold. The Agency stated that this data should be derived from data analysis beyond lot release (i.e. physical structure characterization by NMR, CD, etc).*
- The Sponsor briefly explained that they had conducted extensive Design of Experiment (DOE) work at laboratory scale, but had not submitted this information in their meeting package. The Sponsor said they plan to employ a Quality-by-Design (QbD) approach to support their claim of equivalence between lots manufactured by their intended commercial process and their historical process. Since the details regarding the*

*Sponsor's proposed QbD approach and the mentioned supportive data demonstrating suitability of the QbD approach were not provided prior to the meeting for Agency review, they were not discussed further.*

- *The Agency explained that complete data should be submitted to determine the suitability of using laboratory scale data to address comparability issues between the historical data and the commercial data, as well as the overall acceptability of the proposed QbD approach. The Agency stated that since the Sponsor is proposing a QbD approach for demonstrating comparability, the acceptability of this approach should be addressed in another meeting before submitting the New Drug Application (NDA). The Agency did not agree or disagree with any component of the Sponsor's proposed QbD approach in this meeting, since no QbD information was provided in the initial meeting package. The Sponsor acknowledged this advice and agreed that a separate QbD meeting would be requested in the near future.*

**1b. and 1c. No discussion.**

**QUESTION 2: Does the FDA agree that stability data from the clinical carfilzomib drug substance lots can be used to establish the retest dating period of (b) (4) for commercial drug substance?**

**FDA Response:** No.

- a. None of the clinical drug substance stability lots submitted in your meeting package were manufactured using the intended commercial process and therefore would be considered secondary stability data. Note that the intended commercial manufacturing process for the drug substance differs in suppliers of starting materials, solvents and equipment. Also, the single lot of drug substance which has been manufactured using the intended commercial process is notably different in impurities, residual solvents and optical rotation. No stability data was provided for this lot.
- b. The retest period of the drug substance will be based on evaluation of primary stability lots manufactured using the intended commercial process.
- c. Submit a minimum of 12 months of primary stability data for at least three commercial batches for each strength of the product in the to-be-marketed presentation in the initial submission of your NDA.
- d. Establish a single set of acceptance criteria for release and stability.

**Sponsor reply to FDA response:**

See attached "Response to FDA Preliminary Pre-NDA CMC Meeting Questions" in Appendix 1.

**Discussion:**

**2a, 2b, and 2d. No discussion.**



*2c. The Agency reiterated the recommendation that the Sponsor submit a minimum of 12 months of primary stability data for at least three batches of drug substance manufactured by the intended commercial process.*

**QUESTION 3: Does the Agency agree that for the starting material (b) (4) the analytical tests and controls included in the specification are adequate for a regulatory starting material?**

**FDA Response:** While the specifications and batch analysis results submitted appear to be an acceptable approach to control the quality of starting material (b) (4) for use in manufacturing Phase 3 clinical supplies, there was notable variation in the impurity profiles reported on the four (b) (4) lots manufactured to date - indicating that further development of your intended commercial process is needed to produce material of consistent quality. Also, there was no comparative information provided on the historical lots from supplier (b) (4) to characterize the changes in material arising from the transfer of (b) (4) suppliers (b) (4). Additionally, no lots manufactured by (b) (4), as proposed in your intended commercial process, were submitted. As your manufacturing experience develops, revision of these specifications may be indicated. The final decision regarding acceptability of the specifications for (b) (4) starting material will be an NDA review issue.

**Sponsor reply to FDA response:**

See attached "Response to FDA Preliminary Pre-NDA CMC Meeting Questions" in Appendix 1.

**Discussion:**

*No discussion.*

**QUESTION 4: Does the FDA agree that, for the drug substance, the analytical tests and controls included in the specification are adequate for the NDA?**

**FDA Response:**

There is insufficient batch data produced using your intended commercial process to determine the acceptability of your proposed specification.

- a. Add (b) (4) content to your drug substance specification.
- b. While the final determination of acceptability will be an NDA review issue, the specifications for the drug substance appear to be acceptable for use in Phase 3 clinical supplies. Note that only one lot of drug substance manufactured using the intended commercial process was submitted in the meeting package. As your manufacturing experience develops, revision of these specifications may be indicated.
- c. The acceptance criteria for impurities which are present in the drug substance at levels above the qualification threshold will be an NDA review issue.

**Sponsor reply to FDA response:**

The sponsor agreed to add (b) (4) to the specification and revise the specifications as development progresses. The sponsor also acknowledged that the acceptance criteria will be a review issue. See attached "Response to FDA Preliminary Pre-NDA CMC Meeting Questions" in Appendix 1.

**Discussion:**

*No discussion.*

## **2.2 DRUG PRODUCT**

***QUESTION 5: Does FDA agree that the batch analysis data and manufacturing process comparison between (b) (4) and (b) (4) is adequate to establish that drug product manufactured at (b) (4) is suitable for NDA submission?***

**FDA Response:** Acceptability of the NDA will be based on review of the registration lots of the drug product manufactured by the commercial process with commercial drug substance i.e. commercial lots. You indicate that (b) (4) will manufacture Phase 3 clinical lots and commercial lots. Therefore we advise that you submit at least three registration lots of (b) (4) commercial product in your NDA submission. The batch analysis data and manufacturing process comparison between (b) (4) and (b) (4) non-commercial product submitted in this meeting package indicates that those products are not comparable to future (b) (4) commercial product. Therefore, lots manufactured at (b) (4) and non-commercial lots manufactured at (b) (4) will be secondary and supportive. No commercial product has been manufactured at (b) (4) to date.

**Sponsor reply to FDA response:**

See attached "Response to FDA Preliminary Pre-NDA CMC Meeting Questions" in Appendix 1.

**Discussion:**

*The Sponsor requested clarification on the Agency response. The Agency explained that since the batches of drug product proposed for NDA submission were not manufactured using drug substance manufactured by the intended commercial process, those drug product batches were not suitable for submission. The Sponsor stated that they intend to provide additional data for commercial batches in the NDA.*

***QUESTION 6: Does the FDA agree that for the commercial drug product specification, the tests, analytical procedures, and acceptance criteria included in the specification are adequate for the drug product NDA submission?***

**FDA Response:**

While the final determination of acceptability will be an NDA review issue, the specifications for the drug product appear to be reasonable for use as Phase 3 clinical supplies. Note that no lots of drug product manufactured using the intended commercial process were submitted in the meeting package. As your manufacturing experience develops, revision of these specifications may be indicated. Consider tightening the reconstitution time based on actual and supportive data.

The acceptance criteria for impurities which are present in the drug product at levels above the qualification threshold will be an NDA review issue.

**Sponsor reply to FDA response:**

The Sponsor accepted the preliminary responses. See attached "Response to FDA Preliminary Pre-NDA CMC Meeting Questions" in Appendix 1.

**Discussion:**

*No discussion.*

***QUESTION 7: As the lyophilized drug product formulation and container closure system have not changed, and the lots manufactured at (b) (4) and (b) (4) were produced via an essentially similar process, does the FDA agree that the product shelf life can be established at (b) (4) based on the stability data from representative lots at (b) (4) and up to 6 months stability data for the (b) (4) lots?***

**FDA Response:** No. Expiry will be established based on the stability data from commercial lots of drug product. See response to Question 5.

Establish a single set of acceptance criteria for release and stability.

Table 34: 'Stability Testing Analytical Procedures and Acceptance Criteria' is missing a test for reconstitution time. Include this test in your stability program. The stability data in Appendix 4 includes reconstitution time test results for all lots of drug product submitted.

**Sponsor reply to FDA response:**

See attached "Response to FDA Preliminary Pre-NDA CMC Meeting Questions" in Appendix 1.

**Discussion:**

*No discussion.*

***QUESTION 8: Onyx proposes to present the nominal content on the primary container label for carfilzomib as 60 mg. Does the FDA agree with this label strength?***

**FDA Response:** It is premature to discuss labeling at this time.

**Sponsor reply to FDA response:**

The Sponsor accepted the preliminary response.

**Discussion:**

No discussion.

### **3.0 ISSUES REQUIRING FURTHER DISCUSSION**

**Qdd:** The Sponsor proposes to use a QbD-based approach to reach a process understanding, define process parameters and to demonstrate comparability between the historical and intended commercial product using laboratory scale data. Since no QbD information was provided in the initial meeting package, the Agency recommended that the Sponsor submit another meeting request to further address the comparability issues as well as discuss the overall suitability of the QbD approach. The Sponsor agreed to do so in the future.

### **4.0 ACTION ITEMS**

No action items were identified at this meeting.

### **5.0 ATTACHMENTS AND HANDOUTS**

Appendix 1: "Response to FDA Preliminary Pre-NDA CMC Meeting Questions"  
received 27<sup>th</sup> September 2010

Appendix 2: Presentation: Carfilzomib CMC FDA Type B meeting supporting slides  
presented at meeting, 28<sup>th</sup> September 2010

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/s/  
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SARAH P MIKSINSKI

10/27/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 071057

MEETING MINUTES

Onyx Therapeutics, Inc.  
2100 Powell Street  
Emeryville, CA 94608

Attention: Ted Love, MD  
Executive Vice President, Research & Development

Dear Dr. Love:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Carfilzomib for Injection.

We also refer to the meeting between representatives of your firm and the FDA on August 5, 2010. The purpose of the meeting was to discuss the content and presentation of clinical data in a planned NDA submission.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4256.

Sincerely,

*{See appended electronic signature page}*

Christy Cottrell  
Regulatory Project Manager  
Division of Drug Oncology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

Enclosure

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA  
  
**Meeting Date and Time:** August 5, 2010 at 11:00 am  
**Meeting Location:** WO22, Room 1417  
  
**Application Number:** IND 071057  
**Product Name:** Carfilzomib for Injection  
**Indication:** Multiple myeloma  
**Sponsor/Applicant Name:** Onyx Therapeutics, Inc.  
  
**Meeting Chair:** V. Ellen Maher, MD  
**Meeting Recorder:** Christy Cottrell

### FDA ATTENDEES

Ann Farrell, MD, Supervisory Medical Officer  
V. Ellen Maher, MD, Clinical Team Leader  
Nancy Scher, MD, Medical Officer  
Gideon Blumenthal, MD, Medical Officer  
Angelo DeClaro, MD, Clinical Reviewer  
Hua Lillian Zhang, PhD, Clinical Pharmacology Reviewer, DCP5  
Bijal Pandhi, PharmD, Visiting Clinical Pharmacology Fellow  
CAPT Walter Fava, RPh, MSED, Reviewer, DMEPA  
Christy Cottrell, Regulatory Project Manager

### SPONSOR ATTENDEES

Ruben Sanchez, Associate Director, Regulatory Affairs, Onyx  
Ted Love, MD, Executive Vice President, Research and Development, Onyx  
Michael Kauffman, MD, PhD, Chief Medical Officer, Onyx  
Richard Bryce, MBChB, MRCGP MFPM, Senior Medical Director, Clinical Science, Onyx  
Christopher Kirk, PhD, Vice President, Research, Onyx  
Art DeVault, PhD, Senior Director, Biometrics, Onyx  
Alvin Wong, PharmD, Senior Director, Clinical Science, Onyx  
Alison Cole, Senior Director, Carfilzomib Project Team Leader, Onyx  
Albert Kraus, PhD, Transition Executive, Senior Product Development Advisor, Onyx

### BACKGROUND

The sponsor is proposing to submit an Accelerated Approval NDA based on pivotal study PX-171-003-A1, which is an open-label, single-arm, Phase 2 study of carfilzomib in patients with

relapsed and refractory multiple myeloma. The study evaluates carfilzomib at a dose of 20 mg/m<sup>2</sup> with escalation to 27 mg/m<sup>2</sup> after Cycle 1. The primary efficacy endpoint is Overall Response Rate (ORR) and a total of 266 patients were enrolled.

Supportive studies will include:

- PX-171-003-A0, an open-label, single-arm, Phase 2 study of carfilzomib in 46 patients with relapsed and refractory multiple myeloma at a dose of 20 mg/m<sup>2</sup>
- PX-171-004, an open-label, single-arm, Phase 2 study of carfilzomib in 155 patients with relapsed multiple myeloma
- PX-171-005, a Phase 1b/2 study of the safety and pharmacokinetics of carfilzomib in 50 patients with relapsed and refractory multiple myeloma and varying degrees of renal function
- PX-171-010, an open-label, single-arm, Phase 2 study of carfilzomib maintenance therapy in 43 patients previously enrolled in carfilzomib treatment protocols

Draft responses were sent to the sponsor on August 2, 2010.

## DISCUSSION

1. **Does the Agency agree that the data from Study PX-171-003-A1\*, which includes a derived Overall Response Rate (ORR) of approximately 24% and Duration of Response (DOR) of approximately 8 months (International Myeloma Working Group (IMWG) criteria; to be confirmed by Independent Review Committee [IRC]), provides adequate efficacy data for the filing of an NDA under accelerated approval provisions (21 CFR 314.500; Subpart H) for carfilzomib for the proposed indication: The treatment of relapsed and refractory multiple myeloma in patients who have received at least 2 prior therapies, including a proteasome inhibitor and thalidomide or a thalidomide analog (e.g., lenalidomide)?**

\* PX-171-003-A1—n = 266 with 257 evaluable for efficacy; 9 patients withdrew consent before any drug-related adverse events occurred or prior to obtaining any post-baseline efficacy measurements

**FDA RESPONSE:** Please clarify what is meant by a “derived” ORR. It will be a review issue to determine the adequacy of the data in a single arm trial to support filing for accelerated approval. Carfilzomib must be better than available therapy for the patient population and the ORR reasonably likely to predict clinical benefit.

We note that you have a 0% Complete Response rate. This may be a review issue.

Note that the decision on available therapy is made at the time of NDA action.

**ONYX RESPONSE:** “Derived” ORR and other data were a SAS programming implementation of IMWG criteria. The Independent Review Committee (IRC) results will be presented completely in the NDA where we will compare and contrast the IRC

and derived analyses. The IRC data (21 July 2010) show an ORR of 23.7% including one complete response (CR), 12 (4.7%) VGPR, and duration of response (DOR) of 7.4 months. There are two major points: (1) there is good agreement between the derived and IRC data and (2) the IRC analyses included one complete response (CR). The NDA will include programs and analysis datasets.

**MEETING DISCUSSION:** FDA emphasized that they will also examine the IMWG response rate during review. FDA also emphasized that the ORR must be reasonably likely to predict clinical benefit.

2. Does the Agency agree that data from the clinical trial program provide adequate efficacy data for consideration of the following proposed additional indication in the NDA:

(b) (4)

(b) (4)

**FDA RESPONSE:** No.

(b) (4)

**MEETING DISCUSSION:** FDA recommends a prospectively designed trial to pursue an indication in this subpopulation. Sponsor may submit a plan for such a trial to the FDA for review.

(b) (4)

The evaluation of this claim will be a review issue.

3. Does the Agency agree that the plan for an Integrated Summary of Safety provides adequate safety data to support filing of an NDA under accelerated approval provisions (21 CFR 314.500; Subpart H) for carfilzomib (approximately 700 patients treated with carfilzomib in the safety database and approximately 320 MM patients treated with the dose and schedule intended for marketing)?

**FDA RESPONSE:** The safety database seems adequate.

**ONYX RESPONSE:** No further discussion required.

**MEETING DISCUSSION:** *None.*

4. **Does the Agency agree that the data management plans (i.e., data cutoff dates projected for the second quarter of 2010 according to the statistical analysis plans for Studies PX-171-003-A1 and PX-171-004 driven by preplanned final efficacy analyses at a specific number of treatment cycles after last patient enrolled) and a 90-day safety update plan post-NDA submission are acceptable?**

**FDA RESPONSE:** Please clarify the specific number of treatment cycles (median follow-up) to be assessed after last patient enrolled. We remind you that a 90-day safety update presupposes priority (6 month) review. The determination regarding priority or standard review will not be made until after submission.

**ONYX RESPONSE:** Patients were followed for a minimum of 6 cycles after last patient enrolled in PX-171-003-A1. The first patient enrolled in June 2008. The last patient enrolled in October 2009. The lock for the NDA database occurred in March 2010.

We will submit a 90 or 120 day safety update based on guidance provided by the Agency.

**MEETING DISCUSSION:** *None.*

5. **Does the Agency agree with the proposed primary and secondary analyses in the statistical analysis plan for the pivotal trial (PX-171-003-A1) within the NDA?**

**FDA RESPONSE:** No. You did not specify the method in calculating the 95% confidence interval for ORR in the briefing document and your statistical analysis plan. Pearson-Clopper exact confidence intervals should be used. For potential labeling claims on secondary endpoints, there needs to be adjustment for multiplicity. You did not plan to adjust for multiplicity when testing for secondary endpoints.

**ONYX RESPONSE:** The Pearson-Clopper method will be used to calculate the confidence interval for ORR.

Onyx will review available literature for adjustment for multiplicity of secondary endpoints for single-arm trials.

**MEETING DISCUSSION:** *None.*

6. **Does the Agency agree with the proposal for the data presentation for the Integrated Summary of Efficacy? Are there any other analyses that the Agency requires?**

**FDA RESPONSE:** The proposal for data presentation for the ISE seems acceptable. The Agency does not require additional efficacy analyses at this time. Please include a flag in your datasets for the type of formulation used.

**ONYX RESPONSE:** Onyx will accommodate the Agency's request in the NDA. No further discussion is required.

**MEETING DISCUSSION:** *None.*

7. **Does the Agency agree with the proposal for the data to be included in the Integrated Summary of Safety? Are there any other analyses that the Agency requires?**

**FDA RESPONSE:** The proposal for data presentation for the ISS seems acceptable. Please include a flag in your datasets for the type of formulation used. Please include a flag for all patients who received 20/27 mg/m<sup>2</sup>.

**ONYX RESPONSE:** Onyx will accommodate the Agency's request in the NDA. No further discussion is required.

**MEETING DISCUSSION:** *None.*

8. **Does the FDA agree with the plan, per 21 CFR 314.50(f)(2), to provide patient case report forms (CRFs) for deaths and discontinuations due to adverse events for all studies in the NDA? All other patients CRFs will be available upon request.**

**FDA RESPONSE:** We request that you also provide CRFs for all SAEs. Please also provide narratives for patients who died on study (or within 30 days after study), for patients who discontinued due to adverse events, and for patients who experienced SAEs.

**ONYX RESPONSE:** Onyx will provide all CRFs as requested. Onyx will include narratives for patients who died on study and all SAEs and AEs that led to discontinuation. Onyx had planned to provide narratives for AEs/SAEs of special medical interest (eg, tumor lysis syndrome) as will be defined in the final ISS SAP.

Onyx would like to discuss your request for narratives for all patients who experienced SAEs. A preliminary review indicates this would involve almost all patients in the database (~700).

**MEETING DISCUSSION:** *Sponsor should submit a proposal to identify the SAEs that will be submitted in narrative form. Please submit this within the next several weeks. Please note that if FDA agrees to such a proposal that we may also request additional narratives during the review period.*

9. **Does the Agency agree that a pediatric waiver is appropriate for the proposed indicated patient populations?** (see pediatric waiver justification below)

**FDA RESPONSE:** The request for a pediatric waiver should be made at the time of NDA filing.

**ONYX RESPONSE:** Onyx will include the pediatric waiver in the NDA. No further discussion is required.

**MEETING DISCUSSION:** None.

10. **Does the Agency agree that sending an additional electronic eCTD/sample prior to the NDA submission is not necessary as Onyx has previously submission an eCTD sample (No. 900,434) and 2 electronic INDs in eCTD format (b)(4)?**

**FDA RESPONSE:** We agree that you do not need to submit another eCTD Sample. However, in looking at (b)(4) the ESUB group would like to pass along the following feedback related to your use of attributes in Modules 4 and 5:

- Ensure attributes for module 4 and 5 studies are provided as per page 5 and 6 of the eCTD Backbone File Specification for Study Tagging Files 2.6.1 [PDF] (6/3/2008) <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissions/UCM163560.pdf> which states:

C. Category Element

The category element provides an additional level of study organization not currently provided by the eCTD DTD. This element is only relevant for studies provided in the specific CTD sections cited below.

- 4.2.3.1 Single dose toxicity (grouped by species and route of administration)
- 4.2.3.2 Repeat dose toxicity (grouped by species, route of administration, and duration if applicable)
- 4.2.3.4.1 Long term [carcinogenicity] studies (grouped by species)
- 5.3.5.1 Study reports of controlled clinical studies pertinent to the claimed indication (grouped by type of control)

**ONYX RESPONSE:** Onyx acknowledges the Agency's feedback and will address as appropriate in the NDA.

**MEETING DISCUSSION:** None.

11. **Does the Agency agree with the proposed Table of Contents for the NDA in eCTD format?**

**FDA RESPONSE:** It appears satisfactory.



**ONYX RESPONSE: No further discussion is required.**

**MEETING DISCUSSION:** *None.*

### **ADDITIONAL COMMENTS**

1. The SAS programs that are used to create the derived datasets for the efficacy endpoints and the SAS programs that are used for efficacy data analysis should be included in the NDA submission.
2. Please provide the location of the SAS dataset, the names of the variables used and the programs used to get every new value that will be appearing in the label.

In the appropriate clinical pharmacology sections of the eCTD include the following:

- An evaluation of the effects of covariates such as age, weight, gender, race, etc. on the PK (pharmacokinetics) of carfilzomib.
- Datasets for clinical pharmacology and biopharmaceutics studies should be complete and not be limited to PK/PD. For example, domains related to safety (e.g., ADR's), demographics, non-PK laboratory values, concomitant drug use should be included. All of these are important in identifying patterns of potential clinical pharmacology related causes of clinical safety outcomes.
- Provide all concentration-time and derived PK parameter datasets for all studies. In the study reports, present the PK parameter data as geometric mean with coefficient of variation (and mean  $\pm$  standard deviation) and median with range as appropriate.
- Provide a table listing of patients with renal or hepatic impairment who have received carfilzomib, organized by trial number. Include available renal and hepatic function parameters such as SCr, CLCr calculated by the Cockcroft Gault equation (or eGFR calculated by MDRD), AST/ALT, T.Bili, platelet count, etc for each patient in the listing. Also, provide summaries of the following information for each patient: PK and PD data, safety, and clinical efficacy.
- We encourage you to refer to the following pharmacometric data and models submission guidelines (<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm180482.htm>). For any population PK models all datasets used for model development and validation should be submitted as a SAS transport files (\*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension (e.g.: myfile\_ctl.txt, myfile\_out.txt). A model development decision tree and/or table which gives an overview of modeling steps. For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names

and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

**ONYX RESPONSE: Onyx will perform the analyses as requested. No further discussion is required.**

**MEETING DISCUSSION:** *None.*

DSI has 2 types of requests for data to be submitted to the NDA; one type addresses the clinical data submitted in the NDA that will be used for the inspection as background materials (Items I and II) and the other type addresses the site selection process (Item III).

**Request for general study related information and specific Clinical Investigator information**

A. Please include the following information in a tabular format in the original NDA for each of the completed pivotal trials:

1. Site number
2. Principle investigator
3. Location: City State, Country, to include contact information (phone, fax, email)

B. Please include the following information in a tabular format by site in the original NDA for each of the completed pivotal trials:

1. Number of subjects screened for each site by site
2. Number of subjects randomized for each site by site
3. Number of subjects treated who prematurely discontinued for each site by site

C. Please include the following information in a tabular format in the NDA for each of the completed pivotal trials:

1. Name, address and contact information of all CROs used in the conduct of the clinical trials
2. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
3. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)

### **Request for Site Level Data**

1. For each site in the pivotal clinical trials: Name of primary investigator, accurate address and phone number, e-mail contact
2. For each pivotal trial: Sample blank CRF and an annotated CRF for the site together with the coding key for annotation.
3. For each pivotal trial: Site-specific individual subject data ("line") listings from the datasets:
  - a. Line listings for each site listing the subject/number screened and reason for subjects who did not meet eligibility requirements (i.e., reason for not being randomized/failing screening).
  - b. Line listings by site and subject, of treatment assignment (randomization)
  - c. Line listings by site and subject, of drop-outs and discontinued subjects with date and reason
  - d. Line listings by site of evaluable subjects/ non-evaluable subjects and reason not evaluable
  - e. Line listings by site and subject, of AEs, SAEs, deaths and dates
  - f. Line listings by site and subject, of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
  - g. Line listings by site and subject, of the primary and secondary endpoint efficacy parameters or events.
  - h. Line listings by site and by subject, concomitant medications (as appropriate to the pivotal clinical trials)
  - i. Line listings by site and by subject, of laboratory tests performed for safety monitoring (as appropriate to the pivotal clinical trials)

### **Request for Individual Patient Data Listings format:**

DSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to the attached document, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide datasets in the original NDA application, as outlined, for each pivotal study submitted in your application.

**ONYX RESPONSE:** Onyx acknowledges the Agency's request and will provide the information for PX-171-003-A1.

**MEETING DISCUSSION:** *None.*

### **ISSUES REQUIRING FURTHER DISCUSSION**

None

**ACTION ITEMS**

None

**ATTACHMENTS AND HANDOUTS**

None

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Christy Cottrell  
Regulatory Project Manager  
Minutes Recorder

Concurrence:

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V. Ellen Maher, MD  
Clinical Team Leader  
Meeting Chair

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ND-71057	GI-1	ONYX THERAPEUTICS INC	PR-171

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/

CHRISTY L COTTRELL  
09/01/2010

VIRGINIA E MAHER  
09/07/2010



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** End-of-Phase 2 CMC meeting  
  
**Meeting Date and Time:** August 3, 2009 at 2:00 pm  
**Meeting Location:** WO22, Room 1309  
  
**Application Number:** IND 71,057  
**Product Name:** Carfilzomib (PR-171) for Injection  
**Indication:** Multiple myeloma  
**Sponsor/Applicant Name:** Proteolix, Inc.  
  
**Meeting Chair:** Richard Lostritto, PhD  
**Meeting Recorder:** Christy Cottrell

**FDA ATTENDEES**

Richard Lostritto, PhD, Division Director, ONDQA Pre-Marketing Assessment Branch  
Haripada Sarker, PhD, Pharmaceutical Assessment Lead, ONDQA  
Terrance Ocheltree, PhD, Pharmaceutical Assessment Lead, ONDQA  
Debasis Ghosh, PhD, Chemistry Reviewer, ONDQA  
Anwar Goheer, PhD, Pharmacology/Toxicology Reviewer, DDOP  
Christy Cottrell, Regulatory Project Manager, DDOP

**SPONSOR ATTENDEES**

Lou Sehl, PhD, Director, Chemical Development  
Christopher Kirk, PhD, Director, Biology and Pharmacology  
Evan Lewis, PhD, Principal Scientist, Pharmaceutical Development  
Albert Kraus, PhD, Vice President, Regulatory Affairs and Quality Assurance  
Gary Musso, PhD, Vice President, Operations  
Nazila Habibizad, BS, Senior Manager, Analytical Development

## **BACKGROUND**

The sponsor requested this meeting to discuss and obtain general input and agreement on the following:

### **Drug Substance**

- The Quality by Design (QbD) program
- Validation of the manufacturing process
- Assessment, identification, qualification, and control of impurities
- Proposed release tests

### **Drug Product**

- The QbD program
- Validation of the manufacturing process
- Assessment, identification, qualification, and control of impurities
- Adequacy of stability data to support expiration dating

Draft responses were sent to the sponsor on July 31, 2009.

## **DISCUSSION**

- 1. Does the Agency agree that the scope and focus of the proposed Quality by Design (QbD) program for drug substance is sufficient to establish a control strategy allowing freedom of operation within the defined design spaces independent of scale?**

### **FDA RESPONSE:**

The proposed approach to employ a QbD strategy for the development of drug substance and drug product and establishing control strategies appears to be reasonable. However, note that QbD applies to the knowledge and understanding of the drug substance and product. This includes input factors (such as raw materials and process parameters), process variability, and output factors (such as intermediates), and the final drug substance and product (critical quality attributes). In addition to the lab-scale experimentation on individual unit operations, you should consider how each unit of operation affects other units of operation and the final product (drug substance or drug product). Additionally, you should include information justifying the relevance of the design space developed at small scale to the proposed production scale, see Q8(R1). The design space and application of the design space (e.g., movement within the design space without regulatory notification) are subject to regulatory assessment and approval and will be evaluated during the NDA review. Note that movement within the design space is still subject to Good Manufacturing Practice. Any proposed post-approval regulatory flexibility will be evaluated during the NDA review.

**MEETING DISCUSSION:** *None.*

2. Does the agency agree that the proposed plan for validating the (b) (4) carfilzomib drug substance manufacturing process at (b) (4) utilizing well-characterized and controlled starting materials as defined in the sponsor's plan, is sufficient to support an accelerated NDA?

**FDA RESPONSE:**

The proposed plan for validation appears reasonable however it is too early in the development to make an overall determination of acceptability. We do not agree with the proposed starting materials and recommend that you propose starting materials earlier in your synthesis. See additional comments below regarding any proposed starting materials. It is unclear what you mean by accelerated NDA. Regardless of the review pathway, the requirements for CMC information remain the same.

Additional Comments

Provide the following when proposing the starting materials:

- Impurity profile
- In-house acceptance criteria and Vendor's Certificate of Analysis
- Brief description of synthetic strategies and methods to manufacture
- Detailed discussion on carry-forward impurities
- Controls and Analytical methods to separate and measure appropriate impurities
- Supplier information for the starting materials used to manufacture
- Detailed discussion on purging studies using impurities to demonstrate the ability of the manufacturing process to remove and control the impurities to the desired levels
- Change of control strategies for any potential revisions to the manufacture of proposed starting materials including the vendor's reporting of any changes in starting material specification or controls
- Supportive literature data if available

**MEETING DISCUSSION:** Sponsor slides were discussed in general terms. (b) (4) is acceptable as a starting material. (b) (4) however, is not acceptable as a starting material. (b) (4) should now be designated as an intermediate. Division recommends that the sponsor considers (b) (4) as a new starting material and provide adequate information to establish the purity and identity of this (b) (4) starting material. Two separate validations would be needed: one for 1<sup>st</sup> site for the proposed starting material to intermediate (b) (4) and another for second site for intermediate (b) (4) to drug substance.



**POST-MEETING FOLLOW-UP:** *Process validation involves an objective, scientific demonstration of process control so that batches of active pharmaceutical ingredients (APIs) or drug product consistently meet documented specifications. Process validation is a CGMP requirement for APIs under the Food Drug and Cosmetic Act. This requirement must be met before product is commercially distributed and then maintained during commercialization. The status of process validation is periodically assessed to assure ongoing state of control. Processes must be capable, maintained as stable, and assured by robust monitoring methods to verify the process is in control.*

*We have no objections to your proposed plan for validating the (b) (4) carfilzomib drug substance at (b) (4). The actual protocols, acceptance criteria and study outcomes will be evaluated during an inspection. It is your company's responsibility to conduct all studies necessary to assure your commercial manufacturing process is capable of consistently delivering quality product.*

*A good understanding of the variables, both material attributes and processing parameters, in each unit operation that impact the API's or drug product's specifications and quality attributes, will enable you to generate a sound protocol(s) for the commercial scale performance qualification. For example, your protocol(s) should address the process performance criteria against which you will judge the success of your process validation study(ies). Protocols should also address the data and measurements to be collected, sampling plans, comparisons to be made between individual commercial runs included in the study(ies), and the scientific data analyses, including any statistical analyses, to be performed on all the data collected. A scientific rationale for the protocol design should be available.*

3. **Proteolix considers the proposed drug substance test methods adequate to assure the safety, identity, purity, and quality of the carfilzomib drug substance. Does the Agency agree that the proposed drug substance test methods are acceptable to support Phase 3 clinical studies and an NDA?**

**FDA RESPONSE:**

No. The current acceptance criteria should be modified as greater knowledge is gained during development of the drug product. Tighten the acceptance criteria for Total and Unspecified Impurities. Refer to ICH Q3A for additional guidance. Add tests for heavy metals. Continue testing for Solubility, Optical Rotation and (b) (4). The removal of these from the drug release specification has not been adequately justified. The acceptability of the drug substance specifications will be determined during the review of the NDA.

**MEETING DISCUSSION:** *None.*

4. Does the Agency agree with the proposed plan for impurity identification, classification, and qualification as outlined below? Specifically, regarding:
- a. Acceptability of our identified and qualified process impurities for the drug substance
  - b. Acceptability of our characterization of minor impurities for the drug substance
  - c. Acceptability of our plans for identification of drug product degradation products
  - d. Acceptability of our plans for characterization of degradation pathways.

**FDA RESPONSE:**

The proposed plan for impurity identification, classification, and qualification appears to be reasonable, with some minor exceptions. Impurities that exceed the qualification threshold (b) (4) need to be qualified to ensure the safety of the clinical lots. Another major impurity (b) (4) needs to be reduced by proper process control strategies. Monitoring of (b) (4) is required as part of the control strategy to mitigate the risk. Adequacy will be determined during the NDA review process.

**MEETING DISCUSSION:** Refer to sponsor's slides and submission dated August 12, 2009. DDOP to follow-up.

**POST-MEETING FOLLOW-UP:**

**Sub-Question 4:** Does the Agency agree with Proteolix's assessment that the (b) (4) and other structural isomers of carfilzomib are qualified at current control levels given non-clinical and clinical testing (namely, specification control of (b) (4) respectively)? Monitoring of (b) (4) will be continued as part of the control strategy for the (b) (4) intermediate.

**FDA RESPONSE:** See response to Question 5.

5. Does the Agency agree with the sponsor's assessment of potentially toxic impurities in the drug substance and drug product and the potential genotoxic impurities associated with carfilzomib?

**FDA RESPONSE:**

See response to Question 4. For potentially genotoxic impurities which exceed thresholds outlined in the draft Guidance for Industry Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches, in vitro genotoxicity assay should be conducted. From the information supplied it is not clear that the drug substance batch used

in your genotoxicity studies was adequate to characterize the genotoxic potential of the impurities in your drug substance and drug product.

**MEETING DISCUSSION:** *Refer to sponsor's slides and submission dated August 12, 2009. DDOP to follow up. Sponsor to submit one table with toxicology, genotox data, lot #, impurities, etc.*

**POST-MEETING FOLLOW-UP:**

**Sub-Question 5: Does the Agency agree with Proteolix that genotoxicity risk is appropriately assessed for impurities and potential impurities and that no further non-clinical qualification testing is necessary for the NDA assessment?**

**FDA RESPONSE:** *No. The amount of impurity (b) (4) in the lot used for mouse micronucleus studies (b) (4) was less than in the lots used for chronic toxicity studies (b) (4), Ames and chromosomal aberration studies (b) (4) and the lots used for clinical drug product (b) (4). Therefore, clastogenic activity of carfilzomib in the presence of impurity (b) (4) does not appear to have been properly assessed.*

*The drug product tested for in vitro genotoxic studies (bacterial reverse mutation and mammalian chromosome aberration assays) did not contain (b) (4) (table submitted by the sponsor on 12 August 2009). Therefore, the potential genotoxicity of carfilzomib containing impurity (b) (4) does not appear to be fully characterized.*

6. Does the Agency agree that the scope and focus of the proposed QbD program for drug product is sufficient to establish a control strategy allowing freedom of operation within the defined design spaces independent of scale?

**FDA RESPONSE:**

See response to Question 1.

**MEETING DISCUSSION:** *None.*

7. Does the Agency agree that the proposed drug product manufacturing process validation plan in accordance with Sec. 490.100 Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval (CPG 7132c.08) is acceptable to support an accelerated NDA?

**FDA RESPONSE (provided post-meeting):** Your briefing package states that

*"Proteolix requests the ability to release batches sequentially for commercial distribution prior to completion if all three consecutive validations lots for the manufacturing process..."*

The agency does not approve, disapprove or grant "the ability to release" batches concurrently. Orphan drug status is recognized as a situation where, potentially, distribution of any given lot before completion of the initial process qualification study may be justified. Justification in general is related to market demand at launch, batch size, and expiry periods.

Coverage of process validation activities during a CGMP inspection would include review of study protocols, study execution and data, conclusions, and changes as well as actual market demand and batches distributed and rationale for concurrent release.

With concurrent release, each batch is essentially released on its own merits without the assurance of quality conferred upon product made by a process **proven** to be consistent, reproducible, stable and capable. Your criteria for batch release for this situation will also be reviewed. As the CPG indicates, investigators would be looking for adequate batch controls and testing prior to release for distribution of each batch, a program for monitoring these distributed batches and responding rapidly if information suggests the process is not under control as well as timely assessment of the study data once all the performance qualification or conformance batches have been manufactured. Please adhere to 21 CFR 211.165, Testing and Release for Distribution, which requires in part that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition of their approval and release.

**MEETING DISCUSSION:** *None.*

8. **Does the Agency agree that the stability data from the three identified representative drug product stability lots manufactured by comparable processes (and supported by multiple additional lots) is adequate to support the proposed expiration dating of the drug product in support of an accelerated NDA?**

**FDA RESPONSE:**

See response to Question 2. The use of three representative primary stability lots and supportive stability lots for stability indicating studies appears to be reasonable. However, the data and discussion must be sufficient to demonstrate an understanding of the differences due to the differences in the drug substance, packing size, and manufacturing site. The adequacy of the stability data to support the proposed expiration date will be determined during NDA review based on the stability data submitted in the initial NDA submission.

**MEETING DISCUSSION:** *None.*

**ISSUES REQUIRING FURTHER DISCUSSION**

- Impurities (Q4 and Q5) – addressed in Post-Meeting Follow-Up
- Drug Product manufacturing process validation plan (Q7) - addressed in Post-Meeting Follow-Up

## ACTION ITEMS

Action Item/Description	Owner	Due Date
Sponsor to provide table with impurities, non-clinical/genotox data	Sponsor	August 12, 2009
Sponsor to justify "no cause for concern" (1.5 vs. 0.15)	Sponsor	August 12, 2009
Division to follow-up on Questions 4, 5 and 7	FDA	September 2, 2009

## ATTACHMENTS AND HANDOUTS

Sponsor slides and post-meeting follow-up documentation are attached.

Concurrence: \_\_\_\_\_

Christy Cottrell Regulatory Project Manager Minutes Recorder	Richard Lostritto, PhD Division Director, ONDQA Pre-Marketing Meeting Chair
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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ND-71057	GI-1	PROTEOLIX INC	PR-171
IND-71057	GI-1	PROTEOLIX INC	PR-171
IND-71057	GI-1	PROTEOLIX INC	PR-171

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CHRISTY L COTTRELL  
09/30/2009

RICHARD T LOSTRITTO  
10/01/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

IND 71,057

Proteolix, Inc.  
333 Allerton Avenue  
South San Francisco, CA 94080

Attention: Christine Salido  
Director, Regulatory Affairs

Dear Ms. Salido:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Carfilzomib (PR-171) for Injection.

We also refer to the telecon between representatives of your firm and the FDA on March 30, 2009. The purpose of the meeting was to discuss the study design and assessment of the proposed Phase 3 registrational trial, PX-171-009.

A copy of the official minutes of the telecon is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4256.

Sincerely,

*{See appended electronic signature page}*

Christy Cottrell  
Regulatory Project Manager  
Division of Drug Oncology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes



## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** March 30, 2009  
**TIME:** 2:00 pm  
**APPLICATION:** IND 71,057  
**DRUG NAME:** Carfilzomib (PR-171) for Injection  
**TYPE OF MEETING:** Type C Pre-SPA meeting

**MEETING CHAIR:** V. Ellen Maher, MD, Clinical Team Leader

**MEETING RECORDER:** Christy Cottrell, Regulatory Project Manager

### FDA ATTENDEES:

Robert Justice, MD, Director, Division of Drug Oncology Products  
V. Ellen Maher, MD, Clinical Team Leader  
Nancy Scher, MD, Clinical Reviewer  
Kun He, PhD, Biostatistics Team Leader  
Huanyu Chen, PhD, Biostatistics Reviewer  
Amy McKee, MD, Clinical Reviewer  
Anthony Murgo, MD, Associate Director, Office of Oncology Drug Products  
Christy Cottrell, Regulatory Project Manager

### EXTERNAL CONSTITUENT ATTENDEES:

Michael Kauffman, MD, PhD, Acting Chief Medical Officer  
Albert Kraus, PhD, Vice President, Regulatory Affairs & Quality Assurance  
Christopher Molineaux, PhD, Vice President, Development  
Andres Gutierrez, MD, PhD, Director, Clinical Development  
Christine Salido, Director, Regulatory Affairs  
Scott Cruickshank, MS, Statistical Consultant

### BACKGROUND:

The sponsor is proposing a double-blind, placebo-controlled, Phase 3 study in 610 multiple myeloma patients randomized 1:1 to either carfilzomib/lenalidomide/dexamethasone (LDC) or placebo/lenalidomide/dexamethasone. The primary efficacy endpoint is PFS. This study is intended to provide definitive evidence of clinical benefit.

This meeting was requested by the sponsor to discuss the study design and assessment of the proposed Phase 3 registration trial, which is to be submitted as a Special Protocol Assessment.

Draft responses were sent to the applicant on March 25, 2009.



**MEETING OBJECTIVES:**

Discuss and obtain Agency concurrence on the design and statistical analysis plan for study PX-171-009 prior to a Special Protocol Assessment submission.

**DISCUSSION POINTS:**

1. **Does the Agency agree with the overall scope and design of a randomized, placebo-controlled pivotal trial PX-171-009, including the proposed comparator arm (lenalidomide + dexamethasone)?**

**FDA RESPONSE:**

- This appears generally acceptable. Please justify the planned prolonged duration of induction followed by maintenance and extended maintenance. You should consider re-randomization following induction. Also, please see response to question 5.

***DISCUSSION DURING MEETING:** See discussion under Question 5. FDA withdrew the suggestion regarding re-randomization.*

2. **Does the Agency agree with the assessment of the primary endpoint of PFS by IMWG progression criteria as defined in Appendix D of protocol PX-171-009?**

**FDA RESPONSE:**

- Yes.

***DISCUSSION DURING MEETING:** None.*

3. **Does the Agency agree with the patient population defined in the proposed inclusion/exclusion criteria for PX-171-009?**

**FDA RESPONSE:**

- Yes.

***DISCUSSION DURING MEETING:** None.*

4. **Does the Agency agree that the dose and schedule of dexamethasone proposed for use in both treatment arms of study PX-171-009 is acceptable and appropriate in this relapsed multiple myeloma population?**

**FDA RESPONSE:**

- Yes.

**DISCUSSION DURING MEETING:** *None.*

5. **Does the Agency agree with the proposed duration of carfilzomib treatment of twelve cycles of induction treatment followed by six cycles of maintenance treatment?**

**FDA RESPONSE:**

- We have concerns about your plan for prolonged maintenance treatment. Please provide justification for twelve cycles of induction treatment followed by six cycles of maintenance treatment and possible indefinite extended maintenance. If you wish to evaluate induction and maintenance in the same trial, we recommend that you plan a secondary randomization to maintenance or no maintenance, following the initial period of therapy.

**DISCUSSION DURING MEETING:** *Sponsor clarified that patients will receive 12 cycles of therapy including high frequency carfilzomib or placebo, followed by 6 cycles of therapy including low frequency carfilzomib or placebo. Patients may then continue on Revlimid + dexamethasone alone until disease progression. FDA stated that this is acceptable.*

6. **Does the Agency agree with the proposed stratification factors as outlined in protocol PX-171-009?**

**FDA RESPONSE:**

- Yes.

**DISCUSSION DURING MEETING:** *None.*

7. **Protocol PX-171-009 specifies two preplanned interim analyses of PFS and one final PFS analysis. Does the Agency agree with the statistical analysis plan?**

**FDA RESPONSE:**

- Modified ITT population for primary and secondary efficacy analyses is not acceptable. All efficacy analyses should be based on the ITT population which includes all randomized patients. Other study populations may be used for sensitivity analysis.

**DISCUSSION DURING MEETING:** *Sponsor acknowledged that the ITT analysis would be used as the primary analysis.*

- Please provide more information on OS. With the current sample size, what is the approximate hazard ratio to be detected and what is the power?

**DISCUSSION DURING MEETING:** *FDA advised that a pre-specified analysis plan for OS at the final PFS analysis should be provided. Sponsor stated that at the time of the final PFS analysis, there would be 63% power to detect an increase in OS with a HR of 0.75.*

*Three to four years after the PFS analysis, there would be 80% power to detect a hazard ratio of 0.77. Sponsor has not finalized their plan for the final analysis of OS. This will be specified in the SAP and protocol.*

- The progression events (154, 369, and 461) in your interim analyses by ADDPLAN are different from those based on EAST (155, 376, and 470). Please double check the sample size calculation and alpha allocation.

**DISCUSSION DURING MEETING:** *It seems this discrepancy in numbers is due to different software programs, not trial design and the sponsor plans to move forward with the trial using the ADDPLAN numbers. FDA agreed that this is acceptable.*

- Consideration of PFS as the primary endpoint for demonstration of efficacy for approval of drug products is based on the magnitude of the effect and the risk-benefit profile of the drug product. Because documentation of PFS assessments depends on the frequency, accuracy, reproducibility and completeness of tumor assessments, it is important that the observed magnitude of effect is robust. An early interim PFS analysis (the 1st interim analysis is based on 33% information fraction) may not provide an accurate or reproducible estimate of the treatment effect size due to inadequate follow-up, missing assessments, disagreements between investigator and independent assessments. Therefore, we strongly discourage an early interim analysis for PFS analysis.

**DISCUSSION DURING MEETING:** *FDA clarified that no superiority claim should be made at the first interim analysis. FDA further clarified that it is acceptable to perform a futility analysis and sample size re-estimation at that time. Sponsor indicated that they are no longer planning to do a futility analysis at that time.*

- If you plan to possibly stop the trial early for efficacy claim, it is urged that the nominal significance level for the final analysis not be affected in any way by the futility stopping rule. In current practice, the criteria for stopping for futility reasons are rarely strictly followed. If the alpha spending is affected in any way by considering the presence of futility stopping and the futility stopping rule is not followed, then the overall type I error rate can be substantially inflated to an unacceptable level. On page 327 (15 of 32 in SAP), you stated that “the Sponsor may consider stopping the trial early for overall lack of a treatment difference for PFS” so please pre-specify whether such a rule is binding or nonbinding, and how to adjust the final alpha using repeated CI method. Please also note that, in general, DMC will make an initial recommendation.

**DISCUSSION DURING MEETING:** *Sponsor clarified that they do not plan to perform a futility analysis at the second interim analysis. They do plan to continue to maintain provisions for superiority claims at the second interim analysis (80% progression information). FDA agreed that this is acceptable and no adjustment of final alpha is needed by using the CI method.*

- Please specify detailed criteria for the sample size re-estimation.

**DISCUSSION DURING MEETING:** *Sponsor will be following two parameters: frequency of progression events on the control arm and pattern of enrollment. FDA suggested that the sponsor submit several scenarios. Sponsor will provide the scenarios in the SAP.*

8. **Does the Agency agree that the Proteolix, Inc. plan described in section 10.3.2.8 will provide sufficient safety data to support the initiation of the proposed PX-171-009 clinical trial?**

**FDA RESPONSE:**

- Possibly, if no new safety concerns develop.

**DISCUSSION DURING MEETING:** *None.*

9. **Does the Agency agree that the development program comprised of a single adequate and well-controlled Phase 3 registration trial (PX-171-009) and multiple supporting Phase 1 and Phase 2 trials, could provide adequate safety and efficacy data for acceptance of an NDA (n=approximately 500 in monotherapy safety dataset; n=approximately 360 in combination safety dataset)?**

**FDA RESPONSE:**

- Possibly. We remind you of the following:

For a single randomized trial to support an NDA, the trial should be well designed, well conducted, internally consistent and provide statistically persuasive and clinically meaningful efficacy findings so that a second trial would be ethically or practically impossible to perform.

**DISCUSSION DURING MEETING:** *None.*

**ADDITIONAL COMMENTS**

We require the Statistical Analysis Plan for review at the time of submission of the SPA. We do not currently require or encourage submission of CRFs and Radiology Charters for review at the time of SPA submission.

**DISCUSSION DURING MEETING:** *None.*

**UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:**

None.

**ACTION ITEMS:**

None.

**ATTACHMENTS/HANDOUTS:**

None.

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Christy Cottrell  
Regulatory Project Manager  
Minutes Recorder

Concurrence:

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V. Ellen Maher, MD  
Clinical Team Leader  
Meeting Chair

Linked Applications

Sponsor Name

Drug Name / Subject

-----  
IND 71057

-----  
PROTEOLIX INC

-----  
PR-171

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CHRISTY L COTTRELL

04/28/2009

VIRGINIA E MAHER

04/29/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

IND 71,057

Proteolix, Inc.  
333 Allerton Avenue  
South San Francisco, CA 94080

Attention: Christine Salido  
Director, Regulatory Affairs

Dear Ms. Salido:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PR-171 (Carfilzomib) for Injection.

We also refer to the meeting between representatives of your firm and the FDA on November 6, 2008. The purpose of the End-of-Phase 2 meeting was to discuss the preliminary safety and response data from 77 subjects treated with Carfilzomib for Injection on studies PX-171-003 and PX-171-004.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4256.

Sincerely,

*{See appended electronic signature page}*

Christy Cottrell  
Regulatory Project Manager  
Division of Drug Oncology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** November 6, 2008  
**TIME:** 11:00 am EST  
**LOCATION:** White Oak Campus, Room 1315  
Silver Spring, Maryland  
**APPLICATION:** IND 71,057  
**DRUG NAME:** PR-171 (Carfilzomib) for Injection  
**TYPE OF MEETING:** End-of-Phase 2

**MEETING CHAIR:** Ann Farrell, MD

**MEETING RECORDER:** Christy Cottrell

### FDA ATTENDEES:

Robert Justice, MD, Director, Division of Drug Oncology Products (DDOP)  
Ann Farrell, MD, Deputy Director, DDOP  
Nancy Scher, MD, Clinical Reviewer  
Kun He, PhD, Acting Team Leader, Biostatistics  
Chris Holland, Biostatistics Reviewer  
Julie Bullock, PharmD, Acting Team Leader, Clinical Pharmacology  
Christy Cottrell, Regulatory Project Manager

### EXTERNAL CONSTITUENT ATTENDEES:

Lori Kunkel, MD, Chief Medical Officer and VP, Clinical Development, Proteolix

(b) (4)

Jennifer Lin, Manager, Biometrics, Proteolix

Christine Salido, Director, Regulatory Affairs, Proteolix

(b) (4)

Christopher Molineaux, PhD, VP, Development, Proteolix

Ravi Vij, MD, Principal Investigator

### BACKGROUND:

The sponsor is interested in pursuing accelerated approval of Carfilzomib for Injection as monotherapy for the treatment of multiple myeloma patients who are relapsed/refractory to at least two prior therapies that have included a proteasome inhibitor and a thalidomide/thalidomide analog.

The sponsor is proposing a single-arm pivotal study (PX-171-003) with a primary endpoint of CBR rate [stringent complete response (sCR) + CR + VGPR + PR + MR] of 25% with a sample size of 250 subjects. In addition, the sponsor plans to use studies PX-171-002 and PX-171-004 to provide supportive efficacy and safety data in relapsed and/or refractory multiple myeloma.

In addition, the sponsor is proposing a Phase 3 confirmatory trial (PX-171-009) for conversion from accelerated approval to full approval and for label expansion. The proposed double-blind



trial comparing Carfilzomib/lenalidomide/dexamethasone with placebo/lenalidomide/dexamethasone will have a primary endpoint of progression-free survival (PFS), and will randomize approximately 850 patients with less refractory myeloma. The sponsor plans to submit this Phase 3 confirmatory trial for Special Protocol Assessment in 1Q2009.

Draft responses were sent to the sponsor on October 31, 2008.

#### **MEETING OBJECTIVES:**

Agreement between Proteolix and the Agency on the following:

- Acceptability of study PX-171-003 as a potential registration trial under the accelerated approval pathway per 21 CFR 314.500, Subpart H. The proposed indication for Carfilzomib as monotherapy is for the treatment of multiple myeloma patients who are relapsed and/or refractory to at least two prior therapies that have included a proteasome inhibitor and a thalidomide/thalidomide analog.
- Acceptability of the primary efficacy endpoint of CBR rate as an acceptable endpoint for approval of Carfilzomib for Injection in this relapsed and/or refractory myeloma population under the accelerated approval pathway. CBR rate is defined as stringent complete response (sCR), complete response (CR), very good partial response (VGPR) and partial response (PR) as defined by the International Myeloma Working Group Uniform Response Criteria, plus the additional subcategory of minor response (MR) as defined by the European Blood and Marrow Transplant Group (Blade 1998).
- Acceptability of the planned sample size of 250 subjects to be enrolled in study PX-171-003.
- Acceptability of the proposed Phase 3 confirmatory trial design required for full approval and label expansion.
- Draft Target Product Profile.

#### **DISCUSSION POINTS:**

- 1) Study PX-171-003 (003-A1) is a single-arm, open-label study designed to evaluate the efficacy and safety of carfilzomib as monotherapy in multiple myeloma subjects with relapsed and/or refractory disease. Under 003-A1, refractory disease is defined as lack of tumor response ( $\leq 25\%$  reduction of M-protein) or progression within 60 days after the completion of the subjects' most recent therapy. Relapsed disease is defined as progression greater than 60 days after the completion of the subjects' most recent therapy. Subjects must have disease that is measurable by serum and/or urine protein electrophoresis, and must have received bortezomib and either thalidomide or lenalidomide during the course of their treatment history. The primary efficacy endpoint for this study is CBR rate which includes sCR, CR, VGPR, and PR (as defined by the International Myeloma Working Group Uniform Response Criteria), plus the additional subcategory of MR as defined by the European Blood and Marrow Transplant Group (Blade 1998).

The cumulative multiple myeloma treatment history and response/progression status to the regimen that was received prior to their enrollment on this study will be systematically reviewed and documented by Proteolix, Inc. (and made available to the Agency) to ensure that each enrolled subject satisfies the major eligibility criteria that define the patient population for the proposed indication. Additionally, an Independent Review Committee will evaluate this information and will adjudicate the subject's response status on this study and on their prior therapy. It is anticipated that such quality assurance measures will provide for a single-arm study that is suitably controlled so that the effectiveness data provided from this study can be reviewed and interpreted by the Agency in a meaningful manner.

The rationale for the above design considerations is based on the results from subjects enrolled under the original version of Protocol PX-171-003 (003-A0, closed to enrollment in April 2008). Under 003-A0, a total of 46 subjects with relapsed and/or refractory disease were enrolled, all had relapsed from at least two prior therapies including bortezomib, thalidomide, lenalidomide, corticosteroids, and high-dose chemotherapy with hematopoietic stem cell transplant support. The data from these 46 subjects have shown that carfilzomib is well-tolerated with no study discontinuation or dose reductions due to neuropathy, and infrequent exacerbation of pre-existing peripheral neuropathy (present in 78% of enrolled subjects). In addition, a 26% CBR rate adjudicated by an Independent Review Committee has been observed in this relapsed and/or refractory population. Supplemental data from a supportive, ongoing Phase 2 study PX-171-004, have demonstrated an overall response rate of 54% in the bortezomib naïve group.

Based on the above results, the proposed indication for carfilzomib as monotherapy is for the treatment of multiple myeloma patients who are relapsed and/or refractory to at least two prior therapies that have included a proteasome inhibitor and a thalidomide/thalidomide analog.

- a) **Will the results from the single arm study PX-171-003 (003-A1) of carfilzomib [(20 mg/m<sup>2</sup> Cycle 1 followed by 27 mg/m<sup>2</sup> in subsequent cycles; Days 1, 2, 8, 9, 15, 16 every 28 days) in approximately 250 subjects with multiple myeloma who have failed bortezomib and lenalidomide or thalidomide and the supportive clinical efficacy data from study 003-A0] and PX-171-004 (in which subjects with multiple myeloma were treated with a similar dose (20 mg/m<sup>2</sup>) and the same schedule), be sufficient to file an NDA under the accelerated approval pathway per 21 CFR 314.500, Subpart H for carfilzomib as monotherapy for the treatment of multiple myeloma patients who are relapsed and/or refractory to at least two prior therapies that have included a proteasome inhibitor and a thalidomide/thalidomide analog?**

**FDA RESPONSE:**

- The determination of what constitutes available therapy for a particular population is made at the time of the regulatory action on an NDA. You have not addressed the availability of other drugs which have received regular approval for MM such as melphalan and carmustine.

- Whether the results of a single arm trial will support accelerated approval will also depend on the magnitude of response, duration of response, and the risk-benefit assessment.

#### **PROTEOLIX RESPONSE:**

*Studies 003-A0 and 003-A1 are designed to test carfilzomib in a group of subjects for whom there are no available safe and effective therapies. An examination of the prior therapies administered to subjects enrolled on Study 003-A0 (n=46) highlights the extensive prior therapy administered to enrolled subjects and the data are clinically significant in demonstrating the lack of treatment options remaining for these subjects. All subjects enrolled on Study 003-A0 had failed the recently approved agents for relapsed disease, bortezomib (100%), thalidomide (91%), or lenalidomide (89%) [80% previously received both thalidomide AND lenalidomide]. In addition, 61% of subjects enrolled had previously received all of the common classes of standard of care drugs such as alkylating agents (94%), steroids (100%), anthracyclines (80%), stem cell transplant (83%) and vinca alkaloids (78%). As provided in the patient profiles, subjects often failed multiple chemotherapy combinations. All subjects (100%) have been previously treated with all major classes of agents (proteasome inhibitor, thalidomide, lenalidomide, and steroids) and 83% have received stem cell transplant.*

*To address the use of alkylating agents in greater detail, Proteolix notes that 94% of subjects on Study 003-A0 received at least one alkylating agent, and that physician preference indicates melphalan (89%) and cyclophosphamide (72%) were most commonly utilized and carmustine (BCNU) was rarely used (9%). Subjects may be limited by repeat courses of alkylating agents due to cumulative toxicity, particularly myelosuppression, thereby eliminating use of multiple alkylating agents when considering the risk to benefit ratio.*

#### **DECISIONS REACHED/AGREEMENTS MADE DURING MEETING:**

See discussion under question 2a. The determination whether a single arm trial is acceptable to support accelerated approval is based on data and is a review issue which will not be decided prospectively.

The sponsor will also be submitting the 004 trial data as supportive.

- b) Does the Agency agree that the primary efficacy endpoint of CBR rate 1) as defined in 003-A1 (sCR, CR, VGPR, PR, and MR) and 2) as determined by the Independent Review Committee is an acceptable endpoint for approval of Carfilzomib for Injection for the aforementioned indication under the accelerated approval pathway per 21 CFR 314.500, Subpart H?

#### **FDA RESPONSE:**

- See response to 1a.
- CBR is not acceptable as the primary endpoint, because we do not accept MR. Previous approvals have been based on Blade criteria (CR+PR, but not MR), which

require a duration of at least 6 weeks. International uniform response criteria (Durie et al, Leukemia 2006) could be used: sCR+CR+VGPR+PR. Response should be durable. MR could be captured as a secondary endpoint, also with assessment of duration of response.

- The duration of the response will be critical in assessing the drug's effect.

***PROTEOLIX RESPONSE:***

*The Bladé criteria and International uniform response criteria were primarily developed to assess efficacy in patients with much less refractory disease than those in whom carfilzomib is presently being tested. Proteolix believes that Study 003-A1 will support the increasing body of evidence that in the relapsed and/or refractory population for whom there are no effective treatment options, durable MRs, as well as durable PRs should be taken into consideration. Thus, Proteolix proposes including within the definition for the primary endpoint, a durability component of an MR duration of at least 12 weeks. This would be consistent with the proposal by Anderson et al. (2008) that long lasting MRs in patients with relapse and refractory disease may be a clinically meaningful measure of efficacy for new agents being considered for accelerated approval. In addition, Proteolix will be collecting data on the time to progression, duration of response, and overall survival as well as the median treatment-free interval. This proposal builds on the prior evidence that CRs and PRs correlate with progression free survival and overall survival as demonstrated in the original bortezomib APEX study. As was cited in the Niesvizky 2008 paper, subjects with relapsed disease achieving an MR with the proteasome inhibitor bortezomib had meaningful benefit as demonstrated by a prolonged median treatment-free interval (3.8 vs. 2.3 months), TTP (4.9 vs. 2.8 months), and overall survival (24.9 vs. 18.7 months). Data from Study 003-A0 in which carfilzomib was administered to subjects with relapsed and refractory disease demonstrate that the five MRs are durable (96 days, >183 days, 184 days, >267 days, and >303 days; as of 30 October 2008, median duration of MR is not yet reached) and comparable to that of the five subjects who have achieved PR (>1 day, 117 days, >134 days, 219 days, and 225 days; as of 30 October 2008, median duration of PR is 219 days).*

*Proteolix agrees that the duration of response is critical in assessing carfilzomib's efficacy.*

**DECISIONS REACHED/AGREEMENTS MADE DURING MEETING:**

**The duration of response will be a review issue.**

- 2) The primary efficacy analysis will be based on the primary efficacy endpoint of CBR rate which will be calculated using all subjects enrolled under Amendment 1 (003-A1) that receive at least one dose of study drug (modified intention-to-treat population). The study will be considered successful if the lower boundary of the 95% confidence interval about the CBR rate endpoint exceeds 15%. Based on available data, Proteolix, Inc. anticipates a true CBR rate of 25%. With a sample size of 250 subjects, a one-sample exact binomial test with one-sided significance level of 2.5% will have 97% power to detect a difference between the null hypothesis proportion of 15% versus the alternative proportion of 25%. The study has 80% power if the true CBR rate is as low as 22%. The 46 subjects enrolled under the original version of this protocol (003-A0) will not be included in the analysis of data obtained under 003-A1, but will be analyzed separately and be used as supportive data for approval.

- a) **Does the Agency agree that a CBR rate of 15% represents a clinically meaningful lower boundary from which the success of the trial can be judged?**

**FDA RESPONSE:**

- See the response to question 1b.
- We do not accept CBR as the primary endpoint. In addition, we cannot commit to a fixed rate of response that would be acceptable for approval.

***PROTEOLIX RESPONSE:***

*Proteolix acknowledges the Agency's comments and will take them into consideration. Please refer to Proteolix' reply to question 1b above.*

**DECISIONS REACHED/AGREEMENTS MADE DURING MEETING:**

**The sponsor believes that durable MR (greater than or equal to 12 weeks) represents clinical benefit. FDA stated that the sponsor will need to prove that MR will predict for improvement in quantity or quality of life. The Agency cautioned the sponsor that the percentage of responders is low and that Agency review may alter this number. The sponsor will have to make the case that Carmustine should not be considered "available therapy" for the purposes of accelerated approval.**

- b) **Does the Agency agree with the other parameters and considerations that were used to calculate the sample size for this study?**

**FDA RESPONSE:**

- Yes, using a one-sided exact binomial test is acceptable for sizing the trial. Note, however, that the p-value from this test will not be considered for approval. Rather, the emphasis will be on the rate, the 95% confidence interval around the rate, and the duration of response statistics.

***PROTEOLIX RESPONSE:***

*Proteolix acknowledges the Agency's comments and will take them into consideration.*

**DECISIONS REACHED/AGREEMENTS MADE DURING MEETING:**

**The sponsor would consider planning sample size calculations based on the Summit trial where the lower limit of 90% two-sided confidence interval of ORR must exceed 10%. The FDA stated that the response rate and two-sided 95% CI needed to support approval would be a review issue.**

- 3) The proposed Phase 3 confirmatory trial (PX-171-009) will randomize approximately 850 subjects with less refractory multiple myeloma (1-3 prior regimens) to a double-blind placebo-controlled trial comparing carfilzomib/lenalidomide/dexamethasone with placebo/lenalidomide/dexamethasone and the primary comparative analysis will assess the primary efficacy endpoint of progression-free survival.

**Is the proposed Phase 3 trial acceptable as a confirmatory trial for conversion of accelerated approval to full approval and possible label expansion into a less refractory population?**

**FDA RESPONSE:**

- See responses to previous questions regarding accelerated approval. A phase 3 trial with primary endpoint of PFS in a less refractory population seems acceptable as a confirmatory trial, if accelerated approval proves to be an option, or as a regular approval registration trial.
- The study, as described in the synopsis, appears to have appropriate design characteristics for a Phase 3 trial. However, stopping the trial based on interim PFS analyses is discouraged prior to all patients being enrolled.
- We recommend that the study protocol and statistical analysis plan be submitted for a Special Protocol Assessment prior to study initiation.

***PROTEOLIX RESPONSE:***

*Proteolix acknowledges the Agency's comments and acceptance of PFS as the primary endpoint for this Phase 3 trial as well as acceptance for conduct of this trial in a less refractory population as a confirmatory trial (for an accelerated approval option) or as a regular approval registration trial. Proteolix plans to request a Special Protocol Assessment (SPA) for the proposed Phase 3 Study PX-171-009 protocol, statistical analysis plan, and case report forms (CRFs) prior to study initiation. Proteolix also notes the Agency's comment regarding timing for the interim PFS analyses and will take this recommendation under consideration.*

**DECISIONS REACHED/AGREEMENTS MADE DURING MEETING:**

**No further discussion during the meeting was needed.**

- 4) It is anticipated that approximately 200 to 225 of the 250 subjects enrolled under 003-A1 will receive the lyophilized drug product presentation, Carfilzomib for Injection. The initial 25 to 50 subjects enrolled under 003-A1 are expected to receive the frozen presentation of Carfilzomib for Injection. After reconstitution of the lyophilized drug product with Water for Injection, the quantitative compositions and product attributes of both drug product presentations are equivalent. When the lyophilized presentation of drug product is available, all new subjects enrolling into the study and subjects currently receiving drug will be treated with the lyophilized presentation of the drug product. Please refer to the Agency's meeting minutes dated 1 December 2007 and to Serial No. 0075 dated 19 March 2008, introducing the lyophilized presentation of Carfilzomib for Injection intended for use in clinical studies. The Agency allowed Proteolix, Inc. to proceed with clinical studies provided that the lyophilized GMP lots conform to the drug product specifications and the impurity profiles of the lyophilized GMP lots are comparable to those of the frozen drug product lots.

The proposed analysis of the primary efficacy endpoint (CBR rate) will include all subjects who are enrolled under 003-A1 and receive at least one infusion of Carfilzomib for Injection.

**Does the Agency agree with the proposal to include all 250 enrolled subjects in the primary analysis irrespective of which drug presentation was supplied?**

**FDA RESPONSE:**

- Based upon the agreement made during the December 2007 EOP2 CMC meeting, we agree, from the CMC perspective, that you may proceed with the clinical study provided that the lyophilized GMP lots conform to the drug product specifications and the impurity profiles of the lyophilized GMP lots are comparable to those of the frozen drug product lots. In addition, we recommend that you perform in-use reconstitution/dilution stability studies to confirm that the reconstituted/diluted drug solution meets the proposed specifications if used/stored according to the clinical trial protocol.
- It would be acceptable to include all 250 enrolled subjects in the primary analysis irrespective of which drug presentation was supplied.

***PROTEOLIX RESPONSE:*** *Proteolix acknowledges the Agency's comments and has performed in-use reconstitution/dilution stability studies to confirm that the reconstituted/diluted drug solution meets the proposed specifications when used/stored according to the clinical protocol. Please refer to Serial No. 0075 dated 19 March 2008.*

**DECISIONS REACHED/AGREEMENTS MADE DURING MEETING:**

**No further discussion during the meeting was needed.**

## **ADDITIONAL COMMENTS**

### **CLINICAL PHARMACOLOGY**

Regarding your current protocol (PX-171-009):

1. We recommend that you plan to collect PK data using sparse sampling in your phase 3 protocol (PX-171 009). This would be important in evaluating exposure-response relationships for Carfilzomib for measures of both, effectiveness and toxicity. Please refer to <http://www.fda.gov/cder/guidance/5341fnl.pdf> for more information.

#### ***PROTEOLIX RESPONSE:***

*Proteolix acknowledges the Agency's comments. Proteolix met with the Agency on 30 April 2008 (Type C Clinical Pharmacology meeting) to discuss the clinical pharmacology development plan for carfilzomib. Please refer to the Agency's meeting minutes dated 30 May 2008 and the Agency's minutes in response to Proteolix responses dated 7 August 2008 regarding the Type C Clinical Pharmacology meeting. Proteolix will have a proposed plan for collection of sparse sampling PK to evaluate appropriate exposure response and/or safety relationships with the filing of the SPA request for Study PX-171-009.*

#### **DECISIONS REACHED/AGREEMENTS MADE DURING MEETING:**

**No further discussion during the meeting was needed.**

### **FINAL PROTOCOLS**

If you plan on submitting a request for Special Protocol Assessment, please refer to the May 2002 "Guidance for Industry – Special Protocol Assessment" (posted on the Internet 5/2002) and submit final protocol(s) to the IND for FDA review as a REQUEST FOR SPECIAL PROTOCOL ASSESSMENT (SPA) in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical) and include a reference to this EOP2 meeting. A sample case report form (CRF), the statistical analysis plan, the independent radiologic review charter (if applicable), and the independent data monitoring committee charter should be included. 10 desk copies of this SPA should be submitted directly to the project manager.

Since we may use our ODAC consultant for this protocol review, and their clearance takes several weeks, we would appreciate any lead-in time you could give us as to when the SPA will be submitted. You should also be aware that our using a consultant extends the due date on these SPAs until 45 days after we receive the consultant's written comments.

#### ***PROTEOLIX RESPONSE:***

*Proteolix acknowledges the Agency's comments and plans to request a SPA for the proposed Phase 3 Study PX-171-009 prior to study initiation. The SPA request will include all the requested documents including a study protocol, statistical analysis plan, CRFs, and relevant independent committee charters.*



*In addition, Proteolix plans to request a Type C meeting in advance of filing a SPA request for Study PX-171-009 to discuss the study design in greater detail. Proteolix anticipates the meeting to occur Q1' 2009.*

#### **SUBMISSION OF CLINICAL TRIALS TO NIH PUBLIC ACCESS DATA BASE**

Section 113 of the Food and Drug Modernization Act (Modernization Act) amends 42 U.S.C. 282 and requires the establishment of a public resource for information on studies of drugs for serious or life-threatening diseases conducted under FDA's Investigational New Drug (IND) regulations (21 CFR part 312). The National Institutes of Health (NIH) through its National Library of Medicine (NLM), and with input from the FDA and others, developed the Clinical Trials Data Bank, as required by the Modernization Act.

FDA has made available a final guidance to implement Section 113 of the Modernization Act. The guidance describes the type of information to submit and how to submit information to the Clinical Trials Data Bank. The guidance entitled "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions" was made available on March 18, 2002. It is accessible through the Internet at <http://www.fda.gov/cder/guidance/4856fnl.htm>

The clinical trial information for the Clinical Trials Data Bank should include the purpose of the trial, the patient eligibility criteria, the location of the trial sites and, a contact for patients wanting to enroll in the trial. The data fields and their definitions are available in the Protocol Registration System at <http://prsinfo.clinicaltrials.gov/>. Protocols listed in this system by will be made available to the public on the Internet at <http://clinicaltrials.gov>.

If you have any questions, contact Theresa Toigo at (301) 827-4460 or [113trials@oc.fda.gov](mailto:113trials@oc.fda.gov).

#### ***PROTEOLIX RESPONSE:***

*Proteolix is aware of this requisite and does comply with providing clinical trial information on [clinicaltrials.gov](http://clinicaltrials.gov).*

#### **FINANCIAL DISCLOSURE FINAL RULE**

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective and any study in which a single investigator makes a significant contribution to demonstration of safety.

Please refer to the March 20, 2001 "Guidance for Industry: Financial Disclosure By Clinical Investigators" (posted on the Internet 3/27/2001) at <http://www.fda.gov/oc/guidance/financialdis.html>.

#### ***PROTEOLIX RESPONSE:***

*Proteolix is aware of this requirement and does collect information on financial disclosure by clinical investigators.*

### **PEDIATRIC RESEARCH EQUITY ACT (PREA)**

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

### **PEDIATRIC EXCLUSIVITY**

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at [www.fda.gov/cder/pediatric](http://www.fda.gov/cder/pediatric)) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

### ***PROTEOLIX RESPONSE:***

*Proteolix plans to request a waiver of pediatric studies. Multiple myeloma does not occur in the pediatric population.*

### **DEMOGRAPHICS**

In response to a final rule published 2-11-98, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this analysis. To assist you in this regard, the following table is a suggestion for presentation of the numeric patient demographic information. This data, as well as the pertinent analyses, should be provided in the NDA.

Please provide information for each category listed below from the primary safety database excluding PK studies.

CATEGORY		NUMBER EXPOSED To STUDY DRUG	NUMBER EXPOSED To STUDY DRUG	NUMBER EXPOSED To STUDY DRUG
Gender	Males	All Females		Females >50
Age:	0-≤1 Mo. 12-16	>1 Mo.- ≤ 2Year 17-64		>2-<12  ≥65
Race:	White Other	Black		Asian

**PROTEOLIX RESPONSE:**

*Proteolix acknowledges the Agency's comments and plans to include this analysis within the NDA.*

**QT EVALUATION**

In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Please plan to address this issue early in development.

**PROTEOLIX RESPONSE:**

*Proteolix met with the Agency on 30 April 2008 (Type C Clinical Pharmacology meeting) to discuss the clinical pharmacology development plan for carfilzomib. Please refer to the Agency's meeting minutes dated 30 May 2008 and the Agency's minutes in response to Proteolix responses dated 7 August 2008 regarding the Type C Clinical Pharmacology meeting.*

*As stated previously (refer to Proteolix responses to FDA responses, Serial No. 0083 dated 8 May 2008), Proteolix is aware of and understands the recent FDA Guidance for Industry document (ICH E14 - Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, October 2005) regarding QT/QTc prolongation. Thorough QT/QTc studies cannot be conducted in healthy volunteers with carfilzomib because of safety concerns due to ongoing studies that suggest that carfilzomib induces chromosomal aberrations. Also, please note Proteolix will not be performing placebo controlled single agent clinical studies in the relapsed/refractory subject population.*

*Design elements of collecting triplicate ECGs including baseline and central blind reading were incorporated into Study PX-171-005 in subjects with varying degrees of renal dysfunction and the Phase 1b/2 PX-171-007 study in subjects with relapsed solid tumors. This will include collection of ECGs in a dose range that will capture a low dose (15 mg/m<sup>2</sup>) and a high dose (up*

*to 36 mg/m<sup>2</sup>). In addition, Proteolix will assess the relationship between PK and any changes in ECG parameters with the appropriate PK/PD models. Specifically, Proteolix is collecting the ECG at C<sub>max</sub> and at one hour post infusion and estimate that this will result in approximately 300 individual ECG reads. After completion of these studies, the results will be submitted to the Agency and QT-IRT for review. In addition, a planned drug-drug interaction study will include triplicate ECGs at time points that the Agency recommended in the official meeting minutes dated 7 August 2008.*

**DECISIONS REACHED/AGREEMENTS MADE DURING MEETING:**

**No further discussion during the meeting was needed for the Additional Comments.**

**UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:**

1. Acceptability of the CBR endpoint remains unresolved.
2. Acceptability of a single-arm trial to support accelerated approval will be a review issue.

**ACTION ITEMS:**

1. Sponsor to submit electronic copy of handouts distributed at the meeting. **DONE-  
CSALIDO- 11/7/08**
2. Sponsor to submit Special Protocol Assessment for Phase 3 confirmatory trial PX-171-009.

**ATTACHMENTS/HANDOUTS:**

Slides/handouts distributed by the sponsor at the meeting at attached.

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Christy Cottrell  
Regulatory Project Manager  
Meeting Facilitator/Recorder

Concurrence:

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Ann Farrell, MD  
Deputy Director, DDOP  
Meeting Chair

Linked Applications

Sponsor Name

Drug Name

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IND 71057

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PROTEOLIX INC

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PR-171

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CHRISTY L COTTRELL

11/10/2008

ANN T FARRELL

11/10/2008